PREPARATION AND EVALUATION OF BUCCAL PATCH OF HYDROCORTISONE SODIUM SUCCINATE FOR LOCAL ACTION

Dissertation

Submitted to

The Tamil Nadu Dr. M.G. R. Medical University, Chennai.

In partial fulfillment for the award of the degree of

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In

PHARMACEUTICS

By

Reg No: 26113309

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OCTOBER 2013

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CERTIFICATE

This is to certify that, this thesis work entitled "**PREPARATION AND EVALUATION OF BUCCAL PATCH OF HYDROCORTISONE SODIUM SUCCINATE FOR LOCAL ACTION"** submitted in partial fulfillment of the requirements for the award of degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr. M.G.R Medical University, Chennai is a bonafide work carried out by **Reg No: 2611330**9 and was guided and supervised by me during the academic year Nov 2012-Oct 2013.

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EXAMINERS:

1.

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Acknowledgement

The joyness, satisfaction and euphoria that come along with successful completion of any work would be incomplete unless we mention the people who made it possible whose constant guidance and encouragement served as a beam of light and crowed out efforts.

A sense of triumph is very much justified at this stage of completion of my dissertation. It is a pleasure to utilize this opportunity of acknowledging all those people who have helped me to complete my dissertation.

It is immense pleasure that I take this opportunity to express my heartful thanks and I Dedicate this dissertation work to my husband ***Sunil simon*** *and to my parents* ***Francis and Jassy*** *for their Invincible love, spiritual blessings, illimitable sacrifices and their continous ssupport and motivation throughout my project*

My sincere thanks to my project guide ***Dr.C.Vijaya M.Pharm,Ph.D, Dean and Head of the department, Ultra College of Pharmacy, Madurai,*** *Under his guidance this entire project work was done. I express my profound sense of gratitude for his encouragement observations suggestions co operations in designing and bringing this dissertation work successfully.*

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DECLARATION

I hereby declare that this thesis work entitled **"PREPARATION AND EVALUATION OF BUCCAL PATCH OF HYDROCORTISONE SODIUM SUCCINATE FOR LOCAL ACTION"** submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai was carried out by me in the Department of Pharmaceutics ,Ultra College of Pharmacy, Madurai under the valuable and efficient guidance of **Dr.C.VIJAYA,** Department of pharmaceutics, Ultra College of Pharmacy, Madurai during the academic year Nov 2012-Oct 2013. I also declare that the matter embodied in it is a genuine work and the same has not to formed the basis for the award of any degree, diploma, associate ship, fellowship of any other university or institution.

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CERTIFICATE

This is to certify that the acceptability study on 'PREPARATION AND EVALUATION OF BUCCAL PATCHES OF HYDROCORTISONE SODIUM SUCCINATE FOR LOCAL ACTION' was carried out by Preetha Francis, M.Pharm IInd Year on 10 human volunteers as per the specified protocol (enclosed) under my supervision.

Dr. J. Amba Bhavani, M.D.,
Professor & Head,
Department of Microbiology,
Best Dental Science College,
Madurai.

LETTER OF CONSENT

PREETHA FRANCIS ,IInd M.pharm (pharmaceutics) student has briefed summary of project entitled **PREPARATION AND EVALUATION OF BUCCAL PATCHES OF HYDROCORTISONE SODIUM SUCCINATE IN LOCAL ACTION** and I voluntarily agree to participate in this project.I understand that participation in this study may or maynot benefit.Possible hazards and inconveniences had been explained to my satisfaction.I hereby give my consent for this study.

NAME OF VOLUNTERS	SIGNATURE
1.Preetha Francis	
2.Geethu Susan Georgy	
3.Ratheesh Gopalakrishnan	
4.Deepu Thomas Kurian	
5.B.Masila	
6.Manimekala	
7.Jobu Kuruvilla	
8.Surya Surendran	
9.Bino Babu	
10.Prasanth	

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INTRODUCTION

Administration of the drug via the mucosal layer is a novel method that can render treatment more effective and safe, not only for the topical diseases but also for systemic ones. These unique dosage forms, which can be applied on a wet tissue, are formulated by utilizing the adhesive properties of some water - soluble polymers.

The study shows the anti inflammatory action loaded in the patches which will be reducing the paining of the mouth in adults which compared in different water soluble mucoadhesive polymers.

The mucosal layer lines a number of regions of the body including the gastrointestinal tract, buccal cavity, airways, ear, nose, eye, urogenital tract, vagina and rectum are covered with a thick gel like structure known as mucin, therefore all bio-adhesives must interact with the mucin layer during the process of attachment, these represent the potential sites for attachment of any bioadhesive system.[1,2]

Special features of mucoadhesive dosage forms

- For the drugs with bioavailability problems, they localize the drug in a particular region, there by improving and enhancing the bioavailability[3].
- The strong interaction between the polymer and the mucosal lining of the tissue, help to increase the contact time and permits localization, an essential issue when modification of tissue permeability is important for drug delivery.

  eg:- Peptides, proteins and ionized species.
- To inhibit metabolizing enzymes in a localized area.
- To deliver agents locally for the purpose of modulating antigencity.
- Because of the dual biophysical and biochemical nature of these mucosal membranes, drugs with hydrophilic or lipophilic characteristic can be readily absorbed.

- It has an advantage of bypassing the hepatogastrointestinal first-pass elimination associated with oral administration.

From the view point of drug administration, oral mucosa offers various advantages:

- Because of its accessibility, it permits localization of controlled delivery system and allows opportunity to locally modify tissue permeability, inhibit protease activity or decrease immunogenic response.
- It can be easily removed in case of emergency,
- It offers a passive system which does not require activation.
- It by-passes hepatic first pass metabolism there by offering a greater availability and reduction in dosage.
- It can be made unidirectional to ensure only buccal absorption.
- The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.
- The oral mucosa lacks prominent mucus secreting goblet cells and there by diffusion limited mucus build up over time; beneath a mucoadhesive drug delivery device applied to the oral mucosa does not pose a problem.
- Drug is not subjected to the destructive acidic environment of the stomach and enzymatic alkaline environment of the intestine also, drugs showing poor and erratic absorption from the stomach can be given via this route.
- Therapeutic serum concentration of the drug can be achieved more rapidly.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- Side effects can be reduced by this route which are associated with other routes of drug administration[4,5,6].

Buccal Mucoadhesive Drug Delivery System i.e. the drug delivery via oral mucosa has several advantages.

Which are as follows:

- It avoids the first pass metabolism.
- The absorption of drug is quick and provides immediate relief alternative to the oral route.
- An alternative to injection form7.

Inspite of all these advantages, there are several limitations :

- Once placed at the absorption site the patch should not be disturbed.
- Eating and drinking are restricted until complete absorption has taken place.
- Patient compliance is difficult to achieve.
- Properties like unpleasant taste or odour, irritability to the mucosa, stability at buccal pH etc., pose limitations to the choice of drug, along with their physico chemical limitations[4].

Oral mucosal delivery :

Drugs can be absorbed from the oral cavity through the oral mucosa either sublingually or buccally. In general, rapid absorption from these routes is observed.

The oral cavity is lined by a relatively thick, dense and multilayered mucous membrane with high vasculature. Drugs entering into the membrane can find access to the systemic circulation via network of capillaries and arteries. The arterial flow is supplied by branches of external carotid artery. The venous back flow goes via capillaries and the venous network is finally taken up by the Jugular vein.

The equally developed lymphatic drainage runs more or less parallel to the venous vascularization and ends up in the Jugular ducts. Thus, the buccal & sublingual routes can be used to by- pass hepatic first pass elimination[8].

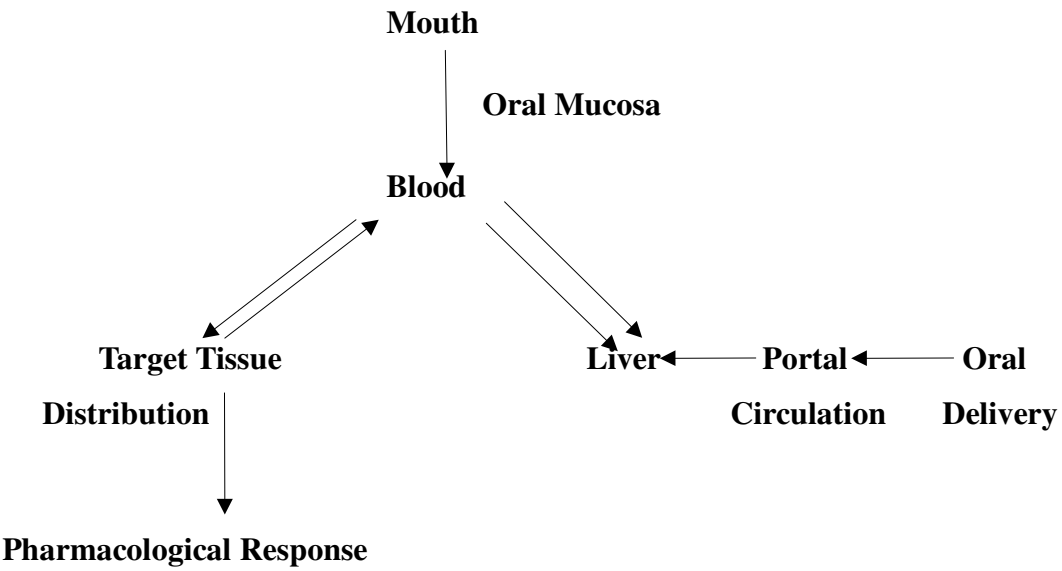


Fig: Drug Absorption In The Oral Cavity

Drug absorption into the mucosa is mainly via passive diffusion into the lipoidal membrane. Compounds with favorable o/w partition coefficient are readily absorbed through oral mucosa. Compounds administered by either the buccal or sublingual routes include steroids, barbiturates, papain, trypsin and streptokinase, streptoclornase. Besides transcellular diffusion, there is evidence that water soluble molecules with molecular volume less than 80 cm^3/mol cross primarily through membrane pores and large water soluble molecules pass paracellularly. Regardless of polarity, large molecules are poorly absorbed[9].

Conventional, buccal and sublingual dosage forms are typically short acting because of limited contact time between the dosage form and the oral mucosa[6]. Since sublingual administration of drugs interfere with eating, drinking and talking, this route is generally considered unsuitable for prolonged administration. On the other hand, the duration of buccal drug administration can be prolonged with saliva activated adhesive troches without the problem of sublingual administration. The polymers that are used are usually water-soluble and will attach to the related tissues or to the surface coating of the tissue. Since these polymers become adhesive upon hydration, they are called wet adhesives.

"Mucoadhesive drug delivery systems may be defined as drug delivery systems which utilize property of bioadhesion of certain water soluble polymers which become adhesive upon hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time."

In general, the permeabilities of the oral mucosa decreases in the order of sublingual >buccal> palatal. The distinct problems that are present in the sublingual route like the drug dissolving in the saliva and unpleasant taste and odour felt by the patient are absent in the buccal mucoadhesive route[3]

A. Human Oral Mucosa:

Oral mucosal delivery has been practiced for many years as evidenced by the development of such pharmaceutical dosage form as sublingual tablets and lozenges. These oral products have been available for several decades and are commonly used for delivering organic based pharmaceuticals to the oral mucosa for either local or systemic medication[10].

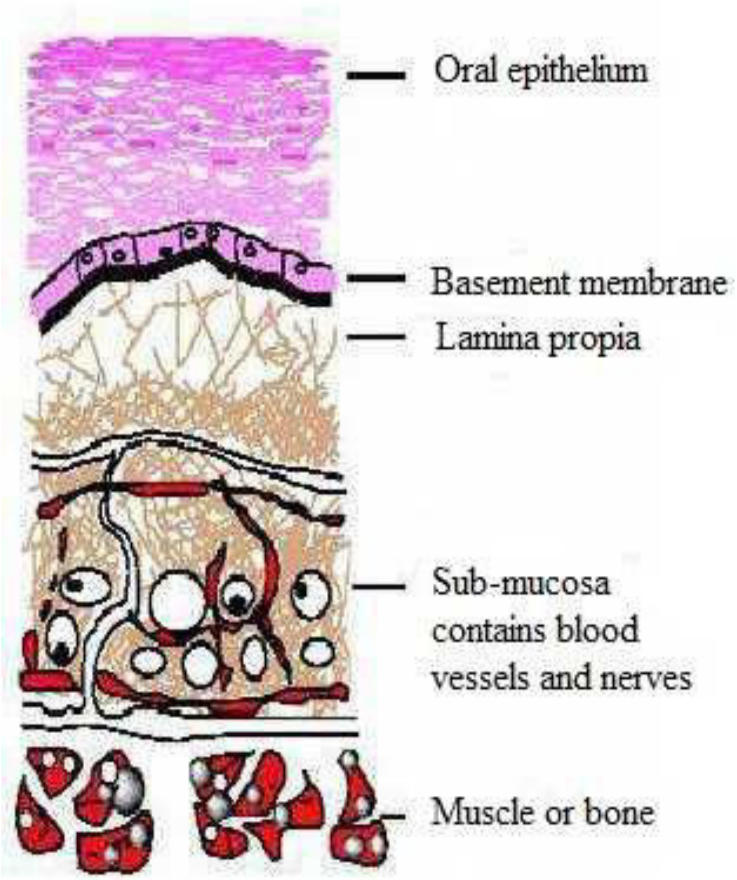


Fig 1: Cross section of oral mucosa

B. Physiological and Anatomical Characteristics of Mucosa:

Oral mucosa is a lining tissue that serves to protect the underlying tissues. It consists of two parts; the underlying epithelium and the connective tissues. The epithelium of the oral cavity is in principle similar to that of the skin, with interesting differences regarding keratinization and the protective and lubricant mucus spread across its surface. The total area is about 100 cm^2, the buccal part with about one third of the total surface is lined with an epithelium of about 0.5 mm thickness and the rest by one of 0.25 mm thickness. The multi-layered structure of the oral mucosa is formed by cell divisions which occur mainly in the basal layer. The mucosa of the oral cavity can be divided into three functional zones.

- The mucus secreting regions consisting of the soft palate, the floor of the mouth, the under surface of the tongue, the labial and buccal mucosa. It has a normally non-keratinized epithelium. These regions are supposed to represent the major absorption sites in oral cavity.

- The hard palate and the gingiva are the regions of masticatory mucosa and have a normally keratinized epidermis.

- Specialized zones and borders of the lips and the dorsal surface of the tongue with its highly sensitive keratinization.

An important feature of the buccal membrane is the presence of numerous elastic fibers in the dermis, which provide its typical elastic and robust behavior.

These fibers represent another effective barrier against the diffusion of drug molecules into the circulation system. The buccal mucosa has also more glycogen granules and numerous ribosomes. The surface of the mucus membrane is constantly washed by a stream of about 0.5 up to 1 lt of saliva daily.

Transport of the drug through oral mucosa is most likely to occur mainly through the non-keratinized sections. The first efficient barrier against penetration, however, is the mucin layer covering the oral epithelium. It consists of glycoproteins. Two transport routes seem to operate by I) Trans cellular route 2) Para cellular route.

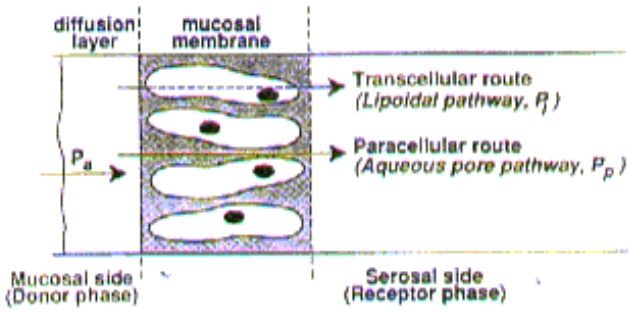


Fig 2: Schematic representation of penetration routes in buccal drug delivary

C. Biochemical Characteristics:

Although the biochemical composition of nasal, rectal and vaginal epithelium has not been well characterized, the lipid composition of other mucosal epithelia, including the buccal mucosa and alimentary tract, have been analyzed.

Mucus is a translucent and viscid secretion which forms a thin, continuous layer adherent to the mucosa epithelial surface. It is secreted by goblet cells, lining the epithelia or by special exocrine glands with mucus cells acini. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the pathophysiological state. However, it has the following general composition.

1. Water - 95%
2. Glycoproteins and Lipids - 0.5 to 5%
3. Mineral salts - 1%
4. Free proteins - 0.5 to1%

D. Mucosol Metabolis:

Drugs may be subjected to metabolism during the course of transmucosal permeation, either in the mucosal surface microenvironment or in the mucosal membrane. Peptidases have been noted to be present in the non-oral mucosa including nasal, rectal and vaginal mucosal homogenates. The ability of the amino peptidases to hydrolyze encephalins was greater in the rectal mucosa than in the nasal and vaginal mucosa

E. Mucosal Membrane Models:

It has been generally accepted that the biological membrane can be represented by Singer and Nicolsan. The following figure is a two dimensional representation of this model, which depicts a biological membrane composed of a fluid state lipid bilayer embedded with globular integral proteins.

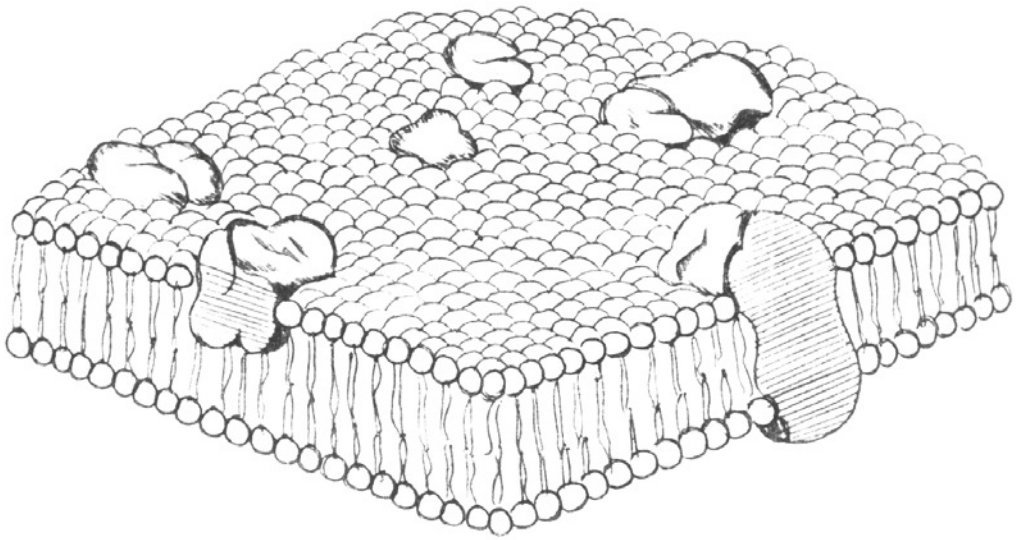


Fig 3: The fluid mosaic model proposed by Singer and Nicolson for the structure of epithelial membrane, consists of amphipathic globular integral protein molecules embedded in the fluid state lipid bilayer.

In the following figure, the integral proteins are shown to be either embedded in a portion of the lipoidal membrane or spanning through out its entire thickness. The amphiphilic protein molecules have been hypothesized to minimize the free energy required for transmembrane permeation by maximizing both hydrophilic and lipophilic interactions in the membrane.

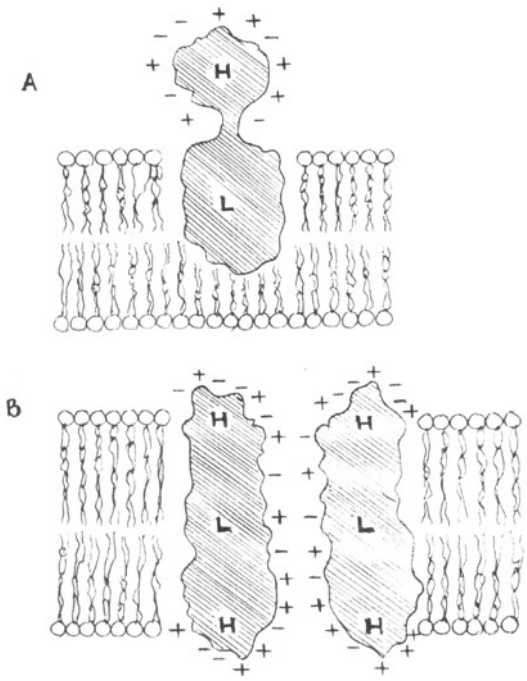


Fig 4: Two thermodynamically favored structures of the globular integral protein molecule.

(A) Monodisperse structure in which the hydrophilic component (H) is exposed to the

aqueous environment on the surface of epithelial membrane and the lipophilic component (L) is embedded in the lipid bilayer.

(B) Subunit aggregate structure in which a subunit aggregate of two protein molecules spanning through the entire thickness of the lipid bilayer to form an aqueous solution filled pore channel[11].

Factors Affecting Buccal Absorption

The oral cavity is a complex environment for drug delivery as there are many dependent and independent factors which reduce the absorbable concentration at the site of absorption.

Membrane factors:

This involves the degree of keratinization, surface area available for absorption, mucus layer or salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute in reducing the rate and amount of drug entering in to the systemic circulation .

Enviornmental factor

- **Saliva**: The thin film of saliva coats throughout the lining of buccal mucosa is called salivary pellicle or film. The thickness of salivary film is 0.07 to 10mm. The thickness, composition and movement of this film effects buccal absorption .

- **Salivary glands:** The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucous on surface of buccal mucosa. Although, mucous helps to retain mucoadhesive dosage forms. It is a potential barrier to drug penetration.

- **Movement of oral tissues:** Buccal region of oral cavity shows less active movement. The muucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods while withstanding tissue

movement during talking and if possible during eating food or swallowing

BIOADHESION

Bioadhesion is an interfacial phenomena in which two materials at least one of which is biological are held together by means of interfacial forces. The attachment could be between an artificial material and biological membrane. In the case of polymer attached to the mucin layer of mucosal tissue, the term mucoadhesion employed.

MECHANISM OF BIOADHESION :

For bioadhesion to occur, a succession of phenomenon whose role depends on the nature of the bioadhesive is required.

- The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface or from the swelling of the bioadhesive.

- In the second stage, after contact is established, penetration of the bioadhesive into the tissue surface of inter penetration of the chains of the bioadhesive with those of the mucus takes place low chemical bonds can then settle.

On a molecular level mucoadhesion can be explained based on molecular interaction. The interactions between two molecules is composed of attraction and repulsion. Attractive interaction arise from vanderwaal forces, electrostatic attraction, hydrogen bonding and hydrophobic interaction. Repulsive interactions occur based on electrostatic and stearic repulsion.

Theories of Bioadhesion:

Several theories have been proposed to explain the fundamental mechanisms of adhesion. In a particular system, one or more theories can equally well explain or contribute to the formation of bioadhesive bonds.

1. Electronic theory:

According to the electronic theory, electron transfer occurs upon contact of an adhesive polymer with a mucous glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

2. Adsorption theory:

According to the adsorption theory after an initial contact between two surfaces, the material adhers because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished.

a. Primary chemical bonds of covalent nature, which are undesirable in mucoadhesion because their high strength may result in permanent bonds.

b. Secondary chemical bonds having many different forces of attraction including electrostatic forces, Vanderwaals forces and hydrogen and hydrophobic bonds.

3. Diffusion theory:

According to diffusion theory, the polymer chains and the mucous, mix to a sufficient depth to create a semitransparent adhesive bond. The exact depth which the polymer chains penetrate the mucous depends on the diffusion coefficient and the time of contact. This diffusion co-efficient, in turn, depends on the value of molecular weight between cross links and decreases significantly as the cross linking density increases.

4. The wetting theory:

This theory is developed predominantly in regard to liquid adhesives, uses interfacial tensions to predict spreading and in turn adhesion. The study of surface energy of both polymers and tissues to predict mucoadhesive performance.

5. The fracture theory:

This theory analyses the forces required to separate two surfaces after adhesion.

The maximum tensile stress (Sm) produced during detachment can be determined by dividing the maximum force of detachment fm , by the total surface area (Ao) involved in the adhesive interaction

$$Sm = fm/Ao.$$

METHODS USED TO STUDY BIOADHESION[2]

Several test methods have been reported for studying bioadhesion. These tests are necessary not only to screen a large number of candidates to mucoadhesives, but also to study their mechanisms. These tests are also important during the design and development of a bioadhesive controlled release system as they ensure compatibility, physical and mechanical liability, surface analysis and bioadhesive bond strength. The test methods can broadly be classified into two major categories.

I). *In- vitro*/ ex- *vivo* methods

II). *In vivo* methods

I): *In – vitro* / ex - *vivo* methods :Most *in- vitro* methods are based on the measurement of either tensile or shear stress, Bioadhesiveness determined by measurement of stress tends to be subjective, since there is no standard test method established for bioadhesion.

1. Methods based on measurement of tensile strength :

These methods usually measures the force required to break the adhesive bond between a model membrane and the test polymers. The instruments usually employed are Modified balance or tensile tester. A typical example is the method employed by Robinson and his group. In this method, the force required to separate the bioadhesive sample from freshly excised rabbit stomach tissue was determined using a modified tensiometer.

2. Methods based on measurement of shear strength :

The shear strength measures the force that causes the bioadhesive to slide with respect to the mucous layer in a direction parallel to their plane of contact. An

example is Wilthemy plate method reported by Smart et al. The method uses a glass plate suspended from a microbalance which is dipped in a temperature controlled mucous sample and the force required to pull the plate out of the solution is determined under constant experimental conditions.

3. Other *in- vitro* methods :

A number of other methods including adhesion weight method , fluorescent probe method, flow channel method, mechanical spectroscopic method, falling liquid film method, colloidal gold staining method, thumb test, adhesion number and electrical conductance method.

II. *In- vivo* methods

Various methods for *in-vivo* evaluation of both placebo and drug containing mucoahesive devices in healthy human volunteers have been reported* since the literature. Rathbone et al" have discussed several methods to study the rate and extent of drug loss from human oral mucosa.

1.4 Factors important to mucoadhesion:

The bioadhesive strength of a polymer or of a series of polymers is effected by the nature of the polymer and also by the nature of he surrounding media.

1. **Polymer related factors**:

   a. **Molecular weight:** The optimum molecular weight for maximum mucoadhesion depends on the type of mucoadhesive polymer at issue. It isgenerally understood that the threshold required for successful mucoadhesion is atleast 1,00,000 molecular weight.

   b. **Concentration of the active polymer:** There is an optimum concentration of a mucoadhesive polymer to produce maximum mucoadhesive in highly concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

c. **Chain flexibility:** Chain flexibility is critical for interpenetration and enlargement. As water soluble polymers become crosslinked, mobility of individual polymer chains decrease and thus the effective length of the chains that can penetrate into the mucous layer decreases, thus reduce mucoadhesive strength.

2. Environment related factors:

a. **pH**: pH can influence the formal charge on the surface of mucous as well as certain ionisable mucoadhesive polymers. Mucous will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Some studies have shown that the pH of the medium is important for the degree of hydration of cross linked polyacelylic acid, showing consistantly increased hydration from pH- 4 to pH - 7 and then a decrease alkalinity and ionic strength increases.

b. **Contact time**: Contact time between the mucoadhesive and mucus layer determines the extent of swelling and interpretation of the mucoadhesive polymer chains. More over, mucoadhesive strength increases as the initial contact time increases.

c. **Swelling** : Swelling characteristics are related to the mucoadhesive itself and its environment. Swelling depends on the polymer concentration, ionic strength as well as presence of water. During the process of mucoadhesion, maximum mucoadhesion *in vitro* occurs with an optimum water content. Over hydration results in the formulation of a wet slippery mucilage without adhesion.

3. **Physiological variable**: Mucin properties, turn over and disease started. In many routes of administration, surface mucous is encountered by the mucoadhesive before it relates the tissue. The extent of interaction between the polymer and the mucous depends on mucous viscosity, degree of entanglement, and water content. How long mucoadhesive remains at the site depends on whether polymer is soluble or insoluble in water and the associated turnover rate of mucin. Estimates of mucin turnover rate widely,

depending on the location and method of measurement. The physicochemical properties of the mucous are known to change during the disease conditions such as the common cold , gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infection of the female reproductive tract, and inflammatory condition of the eye[16].

BUCCAL ADHESIVE DOSAGE FORMS:

Definition

Buccal adhesive dosage forms are those dosage forms which can deliver drugs either locally to treat conditions within the buccal cavity or systemically via the mucosa[13]

Requirement

It often a requirement that buccal-adhesive dosage forms should remain adhesive and allow a controlled delivery of drug for prolonged periods. Therefore, for sustained drug delivery, buccal adhesive formulations must contain elements that remain adhesive for a prolonged period, regulate the rate and direction of drug delivery and, in order to allow both of the above mentioned, restrict the rate of water ingress.

Types of formulations:

Buccal – adhesive dosage forms can be divided into the following types of formulation.

Tablets: Tablets are dry dosage forms that may have to be moistened prior to placing in contact with the buccal mucosa. The size of the tablet is restricted to that which can be comfortably stained in place for prolonged periods.

Films: Buccal patches are two ply laminated system, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing membranes. Three layered tape dosage form has been described that consists of backing layer, a middle layer and an adhesive layer. A bioadhesive multilayered extruded film has also been reported.*

Semisolid preparations: Ointments and gels are most widely used only for localized

drug therapy within the oral cavity.

Powders: These are sprayed onto the buccal mucosa but potential clinical applications of this type of formulation is limited.

Buccal - Mucoadhesive Patches:

Requirement of buccal-adhesive patches:

- They should be flexible enough to allow the movement of the cheek.
- They should be adhesive enough to be retained to the buccal mucosa for at least 6 hours.
- The adhesion should not be so strong, that mucosa is damaged on removal of the patch.
- They should be bio-compatible, non-allergenic and should not cause any irritation.
- The size of the patch may be 10-15 cm^2 in size, but should be 1-3 cm^2 so as to be convenient and comfortable for the patient.
- They should restrict the rate of water ingress.

Successful buccal patch should have following three criterias

a) A bioadhesive to retain drug in oral cavity and maximize the intimacy of contact with mucosa.

b) A vehicle that releases the drug at an appropriate rate under the condition prevailing in the mouth.

c) Strategies for overcoming the low permeability of oral mucosa.

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry :-

TYPE I:

It is a single layer devise with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

TYPE II:

It is a device in which an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double layered device and preventing drug loss from the top surface into the oral cavity.

TYPE III:

It is a unidirectional drug release device, from which drug loss is minu mal, since the drug is released only from the side adjacent to the bucal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

METHODS OF PREPARATION OF PATCHES

Two methods are used to prepare adhesive patches.

1. Solvent casting

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.

2. Direct milling

In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issue.

MUCOADHESIVE POLYMERS

Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks jointed by cross linking agents. The polymer should possess optimal polarity to make sure it is sufficiently wetted by the mucous and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucous to take place.

Many mucoadhesive polymers are made of either synthetic or natural polymers. Most of the current synthetic mucoadhesive polymers are either polyacrylic acid or cellulose derivatives. Examples are carboxy methyl cellulose, carbopol-934P, polycarbophil, tragacanth, sodium alginate, hydroxy ethyl cellulose, hydroxy propyl methyl cellulose, gum karaya, gelatin, guargum, pectin, polyvinyl pyrrolidone, acacia, polyethylene glycol, chitosan and hydroxy propyl cellulose[2].

BUCCAL ABSORPTION ENHANCERS

Penetration enhancers are the substances, which increases the buccal mucosal membrane permeation rate. Although most penetration enhancers were originally designed for the purpose other than absorption enhancement, as systemic search for safe and effective penetration enhancers must be a priority in drug delivery[18].

Examples of membrane permeation Enhancers:

a. Bile salts and other steroidal detergents

Sodium glycocholate

Sodium taurocholate

Saponins.

b. Surfactants

(1) Nonionics:

Polysorbate 80

Sucrose esters

Laureth – 9.

(2) Catoinic:

Cetyltrimethylammonium.

(3) Anionic

Other enhancers

Salicylates

Chelating agents

Sulfoxides.

MECHANISM OF BUCCAL ABSORPTION ENHANCERS :

Mechanism by which penetration enhancers are thought to improve mucosal absorption include the following:

- Changing mucous rheology
- Increasing fluidity of lipid bilayer membrane
- Affecting the components involved in the formation of intracellular junctions.
- Overcoming the enzymatic barrier.
- Increasing the thermodynamic activity of drugs[19].

KINETICS OF DRUGRELEASE:

Generally it is understood that the release of drug from films can be considered as mass transport phenomenon involving diffusion of drug molecules from a region of higher concentration in the dosage form to a region of low concentration in the surrounding environment. The kinetics of drug release from films have been reported and it was assumed that drug release was confined to any of the order such as zero order or first order processes. One indication of mechanism can be obtained using

a plot of log of cumulative percentage of drug remaining in the matrix against time.

First order release would be linear as predicted by following equation.

$$\text{Log } C = \text{Log } Co - Kt/2.303 \quad \text{———-————(1)}$$

Where, C = Amount of drug left in the matrix

Co = Initial amount of drug in the matrix

K = First order rate constant, (time $^{-1}$)

t = time, either in hours or minutes

The *in-vitro* drug release data obtained from all batches of compressed films was treated according to equation (1) by plotting log of cumulative % of drug remaining against time. These plots are shown in results and discussion section.

Next, an attempt was made to see whether the drug release is by diffusion. For systems which will release the drug by diffusion were proposed by Higuchi.

$$Q=[De/T(2A-ec_S)c_St]^{1/2} \quad \text{……(2)}$$

Where, Q = Weight in grams of drug released per unit surface area.

D = Diffusion co-efficient of drug in the release medium. e = Porosity of the matrix.

Cs = Solubility of drug in the films expressed as grams per ml.

The assumption made in the deriving equation (2) are as follows: A pseudo steady state is maintained during release.

A » Cs i.e., excess solute is present.

C = 0 solution at all times (perfect sink).

Drug particles are much smaller than those in the matrix. The diffusion coefficient remains constant.

No interaction between the drug and the matrix occurs.

for the purpose of data treatment, equation is usually reduced to, $Q = Kt^{1/2}$ ----------

(3)

Therefore a plot of amount of drug released verses the square root of time should be linear if the drug release from the matrix is diffusion controlled. For the instances one may control the release from a homogenous matrix by varying the flowing parameters such as:

- Initial concentration of drug in matrix.
- Drug solubility.
- Porosity.
- Tortousity.
- Leaching solvent composition.
- Polymer system making up matrix.

In the present study, the release data obtained were plotted according to the above equation. These graphs are shown in the results and discussion section.

Precisely, to know the exact mechanism of drug release, whether it is by diffusion or with combination of both diffusion and erosion control, the data has also been plotted according to equation as suggested by Korsemeyer. They used a simple empirical equation to describe the general solute release behaviour from control release polymer matrices.

$M_t = Kt^n$ ....(4)

$M\infty$

M_t = the fraction of drug release

$M\infty$

K = Kinetic rate constant t = Release time.

n = Diffusional exponent for drug release.

The value of 'n' gives an indication of the release mechanism. When n=l the release rate is independent of time and is a desirable mechanism in oral controlled drug

delivery, when n=0.5 for fickian diffusion and when 0.5 < n < 1, the diffusion and non fickian transport are implicated.

The *in-vitro* drug release data obtained from all formulations of films was treated according to equation (4) by plotting log cumulative percentage of drug release verses log time. These plots are shown in results and discussion section.

Corticosteroids are the drugs used for the management of many oral inflammatory[40]. Corticosteroids can be administered intradentally, topically or systemically. Intradental or topical corticosteroids are preferred, as those drugs can be administered directly at the site of required action resulting in rapid action and minimal chances of any systemic complications. Topical corticosteroids are widely used and acceptable mode of treatment for vesiculo-erosive diseases of the oral mucosa including oral lichen planus to reduce pain and inflammation. The most acceptable corticosteroid therapy in the management of oral lichen planus is the topical treatment, because it is easier and less expensive than the systemic therapy followed by topical treatment. Corticosteroids are used as dressing agents for cavities and exposed pulp which helps in controlling the inflammatory pulp response and also in reduction of pain [20].

ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis is an insidious, chronic, resistant diseases involving the mucousa, sub mucous or any part of the oral cavity including the pharynx and eosophagus. The disease produces excessive salivation, burning sensation, difficulty in chewing, swallowing and restricted mouth opening in severe cases. Various treatment modalities are used for the treatment of oral submucous fibrosis but application of steroid ointment topically helps in cases with ulcers and painful oral mucosa. Such application have therapeutic effects and mainly shows anti inflammatory activity showing anti inflammatory activity showing a direct healing action on the mucosal patch.

ORAL LICHEN PLANUS

Oral lichen planus is a common mucocutaneous disease. The condition can affect either the skin or mucosa or both causing bilateral white striations. papules or plaques on the buccal mucosa, tongue and gingival.

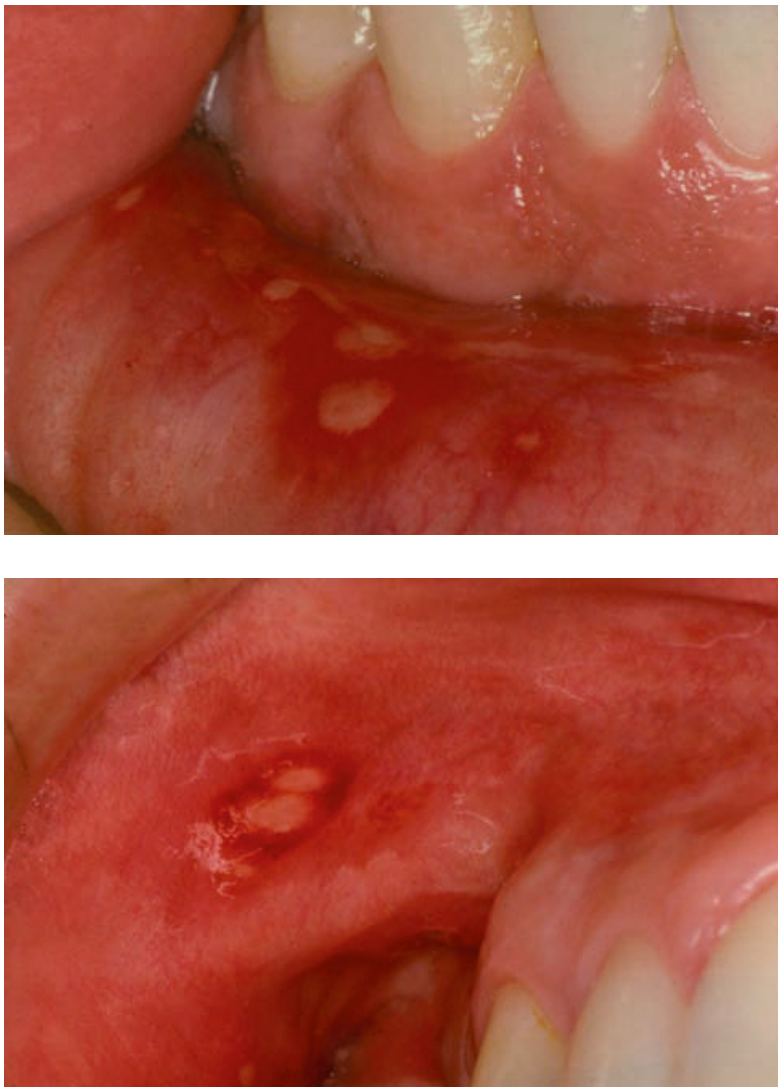


Fig 5: Mucosal diseases

I) STUDIES ON STEROIDS

K.M.K.Masthan et el (2013) reported that the steroids helps in reducing inflammation. Most common types of steroids that are used in dentistry are hydrocortisone, dexamethasone, methyl prednisolone and prednisolone. In dentistry, apart from surgeries, steroids are widely used and accepted mode of treatment for oral mucosal lesions such as oral lichen planus, oral submocous fibrosis, etc.

II) STUDIES ON HYDROCORTISONE SODIUM SUCCINATE

Tank Nimit A et al (2001) reported the formulation and evaluation of fast dissolving tablets of hydrocortisone sodium succinate. It was to prepare FDTs containing hydrocortisone sodium succinate using various super disintergrants by direct compression method in different concentration..all the evaluations were evaluated.

III) STUDIES ON BUCCAL PATCHES

C.Narendra et al (2005) reported the development of three layered buccal compact containing metapropolol tartarate by statistical optimazation technique. The objective of this work to evaluate the effect of formulation variables on release properties and bioadhesive strength in development of three layer buccal compact containing drug,formulation were prepared based on rotatable central composite design with peripheral polymer ratio (carbapol 934P: HPMC 4 KM) and core polymer ratio (HPMC 4 KM : Sodium alginate) as two independent formulation variable.

Nova A.Nafee at al (2003) reported mucoadhesive buccal patches of miconazole nitrate: invitro / in-vivo performance and effect of aging. Mucoadhesive patches containing 10mg, micronazole nitrates were evaluated. The patches were reported with ionic polymer, SCMC and chitosan, non ionic polymers PVA,HEC and HPMC. The convenient bioadhesion, acceptable elasticity, swelling and surface pH were obtained. Patch exhibited sustained release over more than 5 Hrs. and addition of PVA generally enchances the release rate.

The optimum release behaviour was shown with patches containing 10% w/v PVA and 5% w/v PVP.Storage of this patches did not affect the elastic properties, however

enchance the release rate were observed due to marked changes in the crystal habits of the drug.

Vishnu M.patel et al (2007) reported effect of hydrophilic polymers on bioadhesive eudragit patches of propanolol hydrochloride using factorial design. The study was to develop formulations and systematically evaluate invitro performance of buccoadhesive patches of propanolol hydrochloride using hydrophobic polymer eudragit L-100 as the base matrix. The hydrophobic polymer carbapol 934 and polyvinyl pyrolidone (PVP) k-30 were incorporated in to the eudragit patches to provide the patches with bioadhesive properties and to modify the rate of drug release..

Amir H.Shejao et al (1998) reported transbuccal delivery of acyclovir its feasibility, system design and invivo permeation studies. To design buccal mucoadhesive system for systemic delivery of acyclovir was using a novel mucoadhesive, copolymers of acrylic acid and poly (ethylene glycol) and to determine the feasibility of transbuccal delivery of acyclovir.

R.C.Daoijad et al (2006) reported buccoadhesive drug delivery system of isosorbide dinitrate; formulation and evaluation in the form of unidirectional buccal films were developed and characterized for improving bioavailability. Films were formulated by using different bioadhesive polymers like carbapol 934P and polyvinyl pyrolidine by using two different plasticizers propylene glycol and dibutylpthalate and characterized on the basis of their physical characteristic, bioadhesive performance and other parameters.

In vitro studies revealed that the release that the release rate of isosorbid dinitrate was higherfrom carbapol films containing ratio of eudragit RL 100and polyvinyl pyrolidine in proportion of 1:2 and 1:2 respectively by using both plasticizers.

J.Ali et al (2007) reported buccoadhesive erodible disk for treatment of oro-dental infection.Design and characterisation of cetyl pyridinium chloride were prepared by using different bioadhesive polymers along with excipients like mannitol. The in vitro drug release was found to be 94.78% in 6 hrs.In situ release characteristics were evaluated using a flow through assembly,which simulated the conditions of the human buccal cavity.

A.Semalty et al (2005) reported design and evaluation of mucoadhesive buccal films of diltiazem hydrochloride were prepared by solvent casting technique using SCMC,PVP k-30 and PVA and evaluated for their weight, thickness, surface pH, swelling index, in vitro residence time, folding endurance, in vitro release permeation studies and drug content uniformity, films exhibited controlled release over more than 6 hr.

J.Thimmasetty et al (2008) reported design and evaluation of carvidilol buccal mucoadhesive patches, was prepared using HPMC, carbapol 934,eutragit RS100, and ethyl cellulose. The patches were evaluated all the parameters. The invivo drug release studies in rabbits shows 90.85% from HPMC and carbapol patch while it was 74.63 to 88.02% within 90 min in human volunteers.

D.Bhosle et al (2005) reported the design and evaluation of sustained drug release of buccal mucoadhesive patches of chlorhexidine gluconate was prepared using polymer such as HPMC, HES, and PVA by solvent casting method. All the parameters such as were evaluated.

Satish babu B.K.et al (2008) reported the design and evaluation of atenolol patch. The preparation of new bilayered devices comprising a drug containing mucoadhesive and drug free backing membrane. Bilaminated films was prepared by casting method containing the mixture of drug and sodium alginate with **or** without carbapol.

Y.Vamshi Vishnu et al (2007) reported the development of mucoadhesive patches for administration of carvidilol by using two different mucoadhesive polymers. The formulations were evaluated for invitro drug permeation., buccal absorption test, invitro release studies, etc.

Jain-Haw Guo et al formulated Buprenorphine mucoadhesive patch consisting of poly isobutylene, poly isoprene and Carbopol 934p using a two-roll milling method. Carbopol 934p was the bioadhesive of choice for the current formulation because it demonstrated a higher average peeling strength than hydroxyl propyl methyl cellulose, chitosan, or acacia as measured during *in-vitro* testing. *In- vitro* analyses showed that 75% of the buprenorphine was released from the patch following 24 hrs of incubation phosphate buffer at pH -7. It was also shown that patch adhesion increased with increasing thickness and up to three minutes of aging had little effect on adhesive

property.

Ilango R. et al investigated the possibility of obtaining a slow release, relatively constant effective levels of glibenclamide from buccal strips using chitosan. They found that chitosan-based strips of glibenclamide showed better results than Eudragit based glibenclamide buccal strips for controlled release behavior.

Wong C.F., et al fabricated mucoadhesive films using eudragit NE40D and HPMC , SCMC and Carbopol of different grades, and investigated their bioadhesive properties as well as the rate of drug release, using metoprolol tartrate as the model drug. The *in-vitro* drug release was determined using the USP 23 dissolution test apparatus. The bioadhesive properties were evaluated using the texture analyses equipment with chicken pouch as the model tissue. The incorporation of hydrophilic polymers was found to affect the drug release as well as enhanced the bioadhesiveness.

Pandey S., et al prepared buccal mucoadhesive films and mucoadhesive gels of theophylline using hydroxy propyl methyl cellulose, ethyl cellulose and carbopol. The drug release pattern and stability of the formulations were studied and found that the *in-vitro* drug release and *in- situ* intestinal drug absorption were higher with formulations containing carbopol.

Burgalassi S et al prepared and evaluated mucoadhesive patches for controlled release of benzydamine and lidocaine. The patches were prepared by compressing appropriate mixtures containing the drug salts/complexes, a lactose and tamarind gum , were tested *in-vitro* for mucoadhesion and drug release and *in-vitro* on human volunteers for retention and release of benzydamine. The device containing the salts of benzydamine with pectin and polyacrylic acid and the complex of lidocaine with tannicauid showed zero order release kinetics *in vitro*. The patches adhered for over 8hrs to the upper gums of the volunteers and were perfectly tolerated. Benzydamine hydrochloride was released *in vivo* and *in vitro* with practically identical profiles.

Lalla J K.,et al studied permeability co-efficient, flux and other related values of diclofenac potassium through guinea pig buccal mucosa have been compared with those obtained through procaine buccal mucosa at pH 6.8 and 8.0. The permeation value of the species of diclofenac potassium have also been compared with diclofenac

diethyl ammonium salt.Permeability co-efficient values were significantly higher for diclofenac potassium than those for diclofenac diethyl ammonium salt. Use of 5% polysorbate 80 significantly enhanced the permeation of diclofenac potassium.

Noha Adel nafee,et al prepared mucoadhesive patches for delivery of cetyl pyridinium chloride using polyvinyl alcohol, hydroxy ethyl cellulose and chitosan. Swelling and bioadhesive characteristics were determined for both plain and medicated patches. They observed remarkable increase in radial swelling after addition of the water soluble drug to the plain formulae. Polyvinyl alcohol and chitosan containing formulae showed higher drug release as compared to HEC ones. A considerable drop in release was observed for chitosan formulae after the addition of water soluble additives, poly vinyl pyrrolidine and gelatin.

Nafee N.A., et al prepared and evaluated mucoadhesive patches using ionic polymers, sodium carboxy methyl cellulose and chitosan, and non-ionic polymers, polyvinyl alcohol, hydroxy propyl methyl cellulose. Convenient bioadhesion, acceptable elasticity, swelling and surface pH were obtained. Patch exhibited sustained release over more than 5 hrs and the addition of polyvinyl pyrrolidone gently enhanced the release rate. Optimum release behaviour was shown with the patch containing 10% w/v PVA and 5% w/v PVP.

Perioli L,et al prepared mucoadhesive films using several film-forming and mucoadhesive polymers. The film have been evaluated in terms of swelling, mucoadhesion and organoleptic characteristics. The film contained poly vinyl pyrrolidone and carboxy methyl cellulose sodium salt was the best among others. They were loaded with ibuprofen as a model drug and *in-vitro* and *in-vivo* release studies were performed.

SCOPE OF THE WORK

Glucocorticoids can inhibit or suppress the inflammatory responses due to immunological radiant, mechanical, chemical and infectious stimuli thereby having enormous clinical utility[42].

Corticosteroids can be administered intradentally, topically or systemically. In the treatment of oral and buccal inflammatory diseases, intradental or topical corticosteroids are preferred, as those drugs can be administered directly at the site of required action resulting in rapid action and minimal chances of any systemic complications. Topical corticosteroids are widely used and acceptable mode of treatment for vesiculo-erosive diseases of the oral mucosa including oral lichen planus to reduce pain and inflammation. The most acceptable corticosteroid therapy in the management of oral lichen planus is the topical treatment, because it is easier and less expensive than the systemic therapy followed by topical treatment. Corticosteroids are used as dressing agents for cavities and exposed pulp which helps in controlling the inflammatory pulp response and also in reduction of pain[40].

Topical corticosteroids remain the main stay of treatment and management of aphthous ulcers also[43]. Topical corticosteroids are available as oromucosal dissolvable tablets and pastes[44].The commonly used preparations include hydrocortisone hemi-succinate pellets 2.5 mg used 4 times daily, triamcinalone acetonide in carboxy methyl cellulose paste administrated 4 times daily, or β-methasone sodium phosphate as a 0.5 mg tablet dissolved in 15ml of water to make the mouth rinse used 4 times. Especially hydrocortisone preparation is preferred because it does not cause significant adrenal suppression. Hydrocortisone sodium succinate is a natural glucocorticoid which is used for the treatment of any inflammation and its related conditions[43]. Among glucocorticoids, Hydrocortisone sodium succinate is the most suitable drug of choice to be used in the buccal cavity.

Buccoadhesive patches are preferred in the local therapy of these oral lesions as they can deliver the drug to the exact site of action as they are readily attached to the site affected; retained for an appreciable length of time, and removed at any point of time. Earlier, buccal patches of betamethasone sodium phosphate was prepared and investigated for oral submucosal fibrosis[47].

The present study was undertaken to prepare and to evaluate the buccal patches of the hydrocortisone sodium succinate used for the local treatment of the mucosal diseases.

OBJECTIVE OF THE WORK

The main objective of the present work are

- To prepare the buccal patches of the Hydrocortisone sodium succinate with the use of film forming polymer, Eudragit E100, mucoadhesive polymers and a backing membrane.
- To evaluate the formulated patches for various characteristics and properties

PLAN OF THE WORK

Plan of work is outlined below :-

I) Preformulation studies

a. Determination of solubility of drugs

b. Construction of standard curve of Hydrocortisone sodium succinate by UV spectrophotometry

II) Fabrication of buccal patches

a. Preparation and evaluation of drug loaded films

i) Preparation of drug loaded eudragit E 100 films.

ii) Evaluation of films for

a. Thickness

b. Folding endurance

c. Weight variation

d. Content uniformity

e. Surface pH

f. Swelling index

g. Tensile strength

h. Invitro drug release studies

b. Preparation and evaluation of mucoadhessive layer of the patch

1. Preparation of mucoadhessive layer of the patch

a. Carbopol-HPMC film

b.Tamarind

c. Sodium alginate

2. Characterisation of mucoadhessive layer

a. Thickness

b. Weight uniformity

c.Folding Indurance.

d. Swelling Index

e.Mucoadhesive strength estimation

3. Preparation of Buccal patch (laminate) of Hydrocortisone sodium succinate

a. Preparation of EC films (Backing membrane)

b. Preparation of laminate

c. Evaluation

1. ex vivo drug permeation studies.

2. Mucoadhesion studies.

3. In vivo compatibility studies.

MATERIALS AND INSTRUMENTS USED

LIST OF MATERIALS

SL.NO	Chemicals and reagents used	Suppliers
1	Hydrocortisone sodium Succinate	Oman pharmacy
2	Eudragit E 100	Evonik
3	Sodium alginate	Otto chemical biochemica-reagents
4	Carbapol	S.d fine-chem Ltd mumbai
5	Hydroxyl propyl methyl cellulose 15 cps	S.d fine-chem Ltd mumbai
6	Ethyl cellulose	Sd.fine-chem Ltd
7	Poly ethylene glycol 400LR	S.d fine-chem Ltd mumbai
8	Iso propyl alcohol	NICE chemicals P(Ltd) kerala
9	Acetone	SRL
10	Glycerine	Paxmy specialitr chemicals
11	Potassium dihydrogen ortho-phosphate	Otto chemical biochemica-reagents
12	Sodium hydroxide	NICE chemicals P(Ltd) kerala

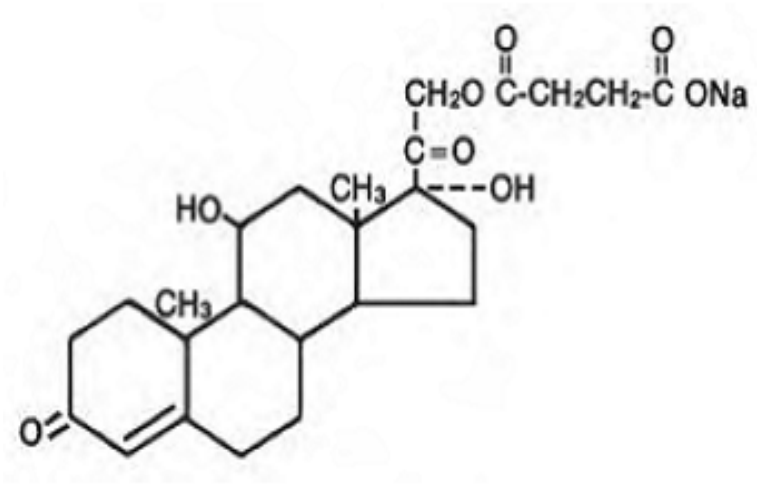
LIST OF INSTRUMENTS

Sl.no	Name of instruments/Equipments	Make and Model

1	Electronic balance	SHIMADZU corporation Japan
2	Dissolution apparatus	LAB INDIA
3	UV-Visible double beam spectrophotometer	SYSTRONICS
4	Bath Ultrasonicator	Confident ultra sonic
5	FTIR	Spectrum RXI
6	Desiccator	Sairam scientific
7	Diffusion cell	Modern scientific
8	Screw gauge	Bakar precision measuring instruments
9	Magnetic stirrer	Remi equipments P(Ltd)
10	Texture Analyser	Stable micro system, UK, TA-XT
11	Heating mantle	Guna Enterprises Chennai
12	Vacuum oven	Shivani scientific industries P(Ltd) Bombay.
13	Micro wave oven	Magic cook Whirlpool

DRUG PROFILE

HYDROCORTISONE SODIUM SUCCINATE [45,46]



Category : Anti-inflammatory, adrenocortical steroids.

Chemical name : Pregn-4-ene-3,20-dione,21-(3-carboxy-1- Oxopropoxy)-11,17 dihydroxy,monosodium salt,(11β).

Mol. Formula : $C_{21}H_{30}O_5$.

Mol.weight : 484.51

Solubility : It is very soluble in water and in alcohol, very slightly soluble incetone and insoluble in chloroform.

Bioavailability : Readily absorbed after oral administration.

Plasma protein binding: 90%

Half life : 1.6 HOURS

Pka value : 5.1

Distribution : crosses placenta, enters breast milk

Tmax : 1 hour

Onset of action : 1-2 HOURS

Elimination **:** In urine

Duration of action : 1-1.5 days

Mechanism of action : Suppresses inflammatory and immune responses, mainly by inhibiting migration of leukocytes and phagocytes and decreasing sinflammatory mediators.

Therapeutic uses:

- Replacement therapy in adrenocortical insufficiency.
- Hypercalcaemia due to cancer.
- Arthritis.
- Collagen diseases.
- Dermatological diseases.
- Autoimmune and haematologic disorders.
- Ulcerative colitis.
- Multiple sclerosis.
- **In dental :** Treatment of a variety of oral diseases of allergic, inflammatory or auto immune origin.

Side effects:

- Stomach upset.
- Head ache.
- Dizziness.
- Menstrual period changes.
- Trouble sleeping.
- Increased appetite.
- Weight gain.
- Pain/redness/swelling at the site of injection.

Contraindications

- Hypersensitivity to drug, alcohol, bisulfites, or tartrazine (with some products)
- Systemic fungal infections
- Concurrent use of other immunosuppressant corticosteroids
- Concurrent administration of live-virus vaccines

Precautions

Use cautiously in:

- hypertension, osteoporosis, glaucoma, renal or GI disease, hypothyroidism, cirrhosis, thromboembolic disorders, myasthenia gravis, heart failure
- pregnant or breastfeeding patients
- children ages 6 and younger.

Drug-drug Interactions :-

Amphotericin B, loop and thiazide diuretics, mezlocillin, piperacillin, ticarcillin :-

additive hypokalemia

Fluoroquinolones :- increased risk of tendon rupture

Hormonal contraceptives :- prolonged half-life and increased effects of hydrocortisone

Insulin, oral hypoglycemic :- increased requirements for these drugs

Live-virus vaccines :- decreased antibody response to vaccine, increased risk of adverse reactions

Nonsteroidal anti-inflammatory drugs :- increased risk of adverse GI reactions

Phenobarbital, phenytoin, rifampin :- decreased hydrocortisone efficacy

Somatrem :- inhibition of growth-promoting effect

Dose :-

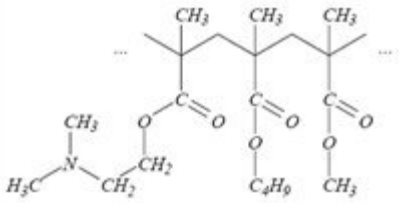
Injection	:	25 mg/ml, 50 mg/ml; 100 mg/vial, 250 mg/vial, 500 mg/vial, 1,000 mg/vial
Intrarectal aerosol foam	:	90 mg
Oral suspension	:	10 mg/5 ml
Retention enema	:	100 mg/60 ml
Spray (topical)	:	1%
Tablets	:	5 mg, 10 mg, 20 mg

EUDRAGIT E 100

EUDRAGIT® E 100 is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate.

Physical Description: Itconsists of colourless to yellow tinged granules with a characteristic amine-like odor.

Chemical structures:



Product Form: Granules

Targeted Drug Release Area: Stomach

Dissolution:

- Soluble in gastric fluid up to pH 5.0
- Swellable and permeable above pH 5.0

Characeristics:

- Low viscosity, high pigment binding capacity, good adhesion
- low polymer weight gain

Chemical/ IUPAC name: Poly(butyl methacrylate-co-(2- demethylaminoeethyl) methacrylate-co-methyl methacrylate) 1:2:1

Weight average molar mass: Mw approx. 47,000 g/ mol
Alkali Value: 180 mg KOH/ g polymer

Glass Transition Temperature (Tg): ~ 48°C

Solubility : Soluble in acetone, ethanol, methanol, propanol, dichloromethane. ethyl acetate. Insoluble in water and petroleum ether.

Category : Film former, tablet binder, tablet diluent.

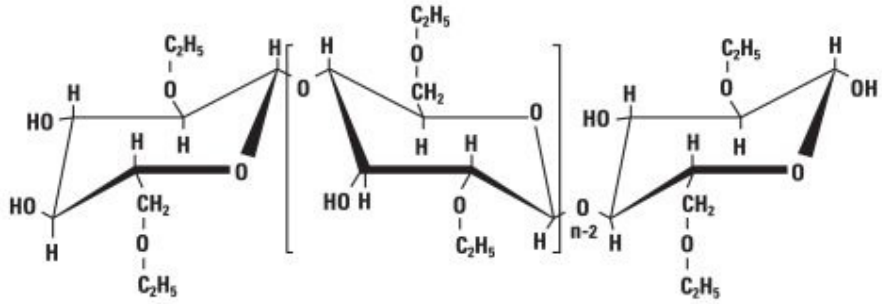
Polymer Profile

Ethyl cellulose (EC)

Synonyms: Aquacoat E-462, Ethocel, Surelease.

Functional category: Coating agent, tablet binder and viscosity increasing agent.

Structural formula:



Description: Ethyl cellulose is a tasteless, free flowing white light coloured powder.

Solubility:

1. Ethylcellulose is practically insoluble in glycerin, propylene glycol and water.
2. EC that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol, ethyl acetate, methanol and toluene.

Melting point: Glass transition temperature – 129-133ºC

Stability and Storage Conditions: Ethyl cellulose is stable, slightly hygroscopic materials. It is subjected to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. It should not be stored at temperature exceeding 32ºC (90ºF).

Safety: Ethyl cellulose is widely used in oral and topical pharmaceutical formulations. It is not metabolized following oral consumption and is therefore a non-calorific substance. Ethyl cellulose is generally regarded as non-toxic, non- allergic and non-irritating material.

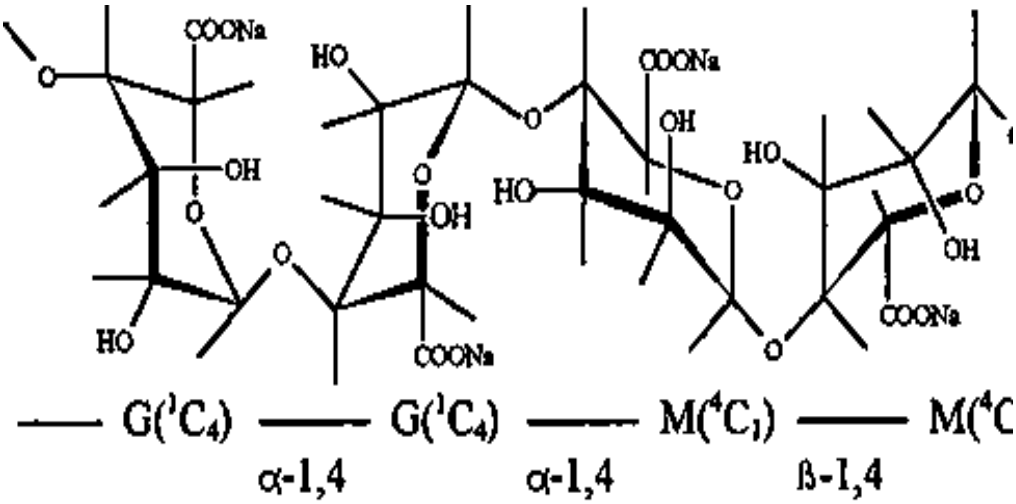
Handling Precautions: It is important to prevent fine dust clouds of ethyl cellulose from reaching potentially explosive levels in air. Ethyl cellulose is combustible. EC powder may be an irritant to the eyes and eye protection should be worn

SODIUM ALGINATE

DEFINITION :- Sodium alginate is the sodium salt of alginic acid.

Chemical formula :- $(C_6H_7NaO_6)_n$

Structural formula :-



DESCRIPTION :- Occurs as white to yellowish brown amentous, grainy, granular or powdered forms

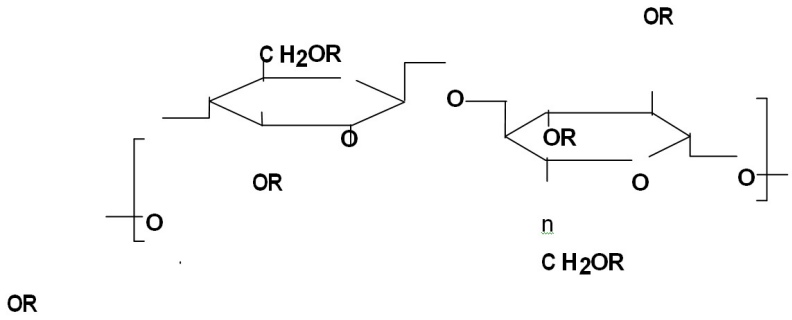
FUNCTIONAL USES :- Stabilizer, thickener, gelling agent, emulsifier

SOLUBILTY :- Dissolves slowly in water, forming a viscous solution; insoluble in ethanol and ether

DENSITY :- 1.601 g/cm^3

HYDROXY PROPYL METHYL CELLULOSE

It is a mixed alkyl hydroxy alkyl cellulose ether and may be regarded as propylene glycol of methylcellulose.



where R is H, CH_3 or $[CH_3CH(OH)CH_2]$

Chemical name : Cellulose, 2-hydroxypropyl methyl ether.

Emperical formula : $C_8H_{15}O_6$ - $(C_{10}\text{-}H_{18}O_6)n$ – $C_8H_{15}O_5$.

Grades : Methocel - E5, E15, E50, E4M, F50, F4M, K 100, K4M, K15M, K 100M.

Description : Odourless, tasteless, white or creamy fibrous or granular powder. **Molecular weight:** Approximately 86.000.

Density : 0.25 - 0.70 gm/cm^3

Viscosity : HPMC E15 CPS (2% aqueous solution, HPMC EYM 4000 CPS aqueous solution).

pH : 6.0-8.0 (1% aqueous solution).

Solubility: Soluble in cold water, forming a viscous colloidal solution. Insoluble in ether, alcohol and chloroform. But soluble in mixtures of methanol and methylene chloride. Certain grades are soluble in aqueous acetone, mixtures of methylene chloride and isopropyl alcohol and other organic solvents.

Stability : Very stable in dry conditions.

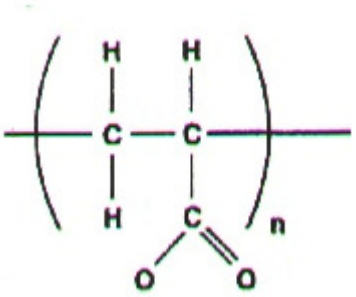
Safety : Hydroxy propyl methyl cellulose has been shown to be safe in humans and in animals.

Incompatibility : It is incompatible at extreme pH conditions and in the presence of oxidizing materials.

Applications : It is used as suspending, viscosity increasing and film forming agent. It is also used as a tablet binder and as an adhesive ointment ingredient. The E grades are generally suitable as film formers and K grades are used as thickeners.

CARBOPOL 940 LR

Chemical structure :-



SYNOYM : Carbomer

Chemical name : Carboxyvinyl Polymer; average equivalent weight: ca.76; Bulk density: 0.20-0.23 g/cm3; pH (0.5% water dispersion): 2.7-3.5

Carbomer is a fine white acrylic powder used in hair gels, and other gels, lotions, and creams.

It is suitable for formulating sparkling and clear gels as well as stabilizing emulsions. The typical use level is 0.1-0.5% depending o n the type of formulation and final desired viscosity.

It is a cost effective thickener and is pH sensitive. Carbomer must be thoroughly mixed and hydrated. Increasing the pH to 7.0, gives a gel structure. Neutralization can be carried out with inorganic bases (such as NaOH, KOH, NH4OH) or with organic amines (such as TEA, AMP, AMPD). To neutralize 1 g of Carbomer to pH 7, ca. 0.01 equivalent of base are required (e.g. 0.4g of NaOH, 0.9g of AMP, 1.5g of TEA). It is advisable to add strong bases previously diluted into water at a concentration not higher than 10%.

Solubility : Soluble in water, alcohol and glycerine.

Stability : Gel loses viscosity upon exposure to sunlight. It is relatively unaffected by temperature variations and is resistant to bacterial growth.

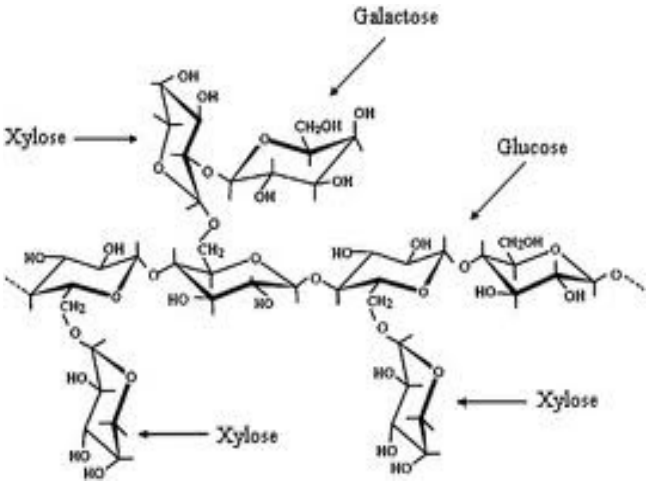
Safety : It is safe and non-toxic. No primary irritation or allergic reaction in human beings upon topical application. It is not absorbed in the body and is excreted unchanged. It contributes no off-taste and in some cases may mask the undesirable taste of formulation.

TAMARIND GUM

Synonyms : Tamarindus indica linn.

Molecular weight : Within the range of 2.5×10^5 and 6.5×10^5.

Structural Formula :



Functional category : stabilizer,thickener,gelling agent,and binder in food and pharmaceutical industries.

Pharmaceutical application :

- Dissolution improvement
- Nasal mucoadhesion

METHODS

PREPARATION OF STANDARD CURVE OF HYDROCORTISONE SODIUM SUCCINATE[41].

Procedure :-

The accurately weighed quantity of 100 mg of hydrocortisone sodium succinate was dissolved in 100 ml of phosphate buffer pH(6.8) as stock solution A and then from this solution 1ml was pippeted out and diluted with phosphate buffer (pH6.8) up to100ml,this solution as stock solution B 1, 2, 3, 4, 5 , 6, 7, 8, 9,and ml 10 ml pipettedin different 10ml volumetric flasks. These were finally diluted up to 10ml phosphate buffer (pH 6.8).

Absorbance of each of these was recorded at 249 nm.

The absorbance was plotted against concentration; a straight line passing through origin was obtained which indicate that concentration of dilutions obeys the Beer-Lamberts law

PREPARATION OF TAMARIND SEED POLYSACCHARIDE SOLUTION.

Take the required quantity of tamarind in distiiled water and boiled in water bath. After that the solution keep in 24hrs and filtered this solution.

FABRICATION OF BUCCAL PATCHES.

The patches were prepared by solvent casting.

SOLVENT CASTING METHOD

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.

FABRICATION OF DRUG MATRIX DEVICE

For the formulation D1 and D2 accurately weighed quantity of hydrophobic polymer Eudragit E 100 dissolved in isopropyl alcohol and acetone in the ratio of 6:4. The accurately weighed quantity of hydrocortisone sodium succinate dissolved in the above polymer solution, the solution was mixed according to required proportion. The required quantity of poly ethylene glycol 400 was added as plasticizer, after which the solution was poured in to the petridish and it is dried in the drier.

FABRICATION OF MUCOADHESIVE LAYER

Mucoadhesive polymers are sodium alginate, tamarind gum and carbapol, HPMC combination which are dissolved in water and added glycerine as a plasticizer. Then the solution are poured in the petridish and kept in vaccum oven.

FABRICATION OF BACKING MEMBRANE.

The backing membrane used as ethyl cellulose film in which ethyl cellulose is dispersed in toluene and glycerine as plasticizer.

FABRICATION OF BUCCAL LAMINATES.

The laminates was prepared by using the drug loaded film placing between the mucoadhesive layer and the backing membrane.

Table 1: COMPOSITION OF BUCCAL PATCHES LAMINATE FORMULATIONS.

Formulation code	D1 (mg)	D2 (mg)
Hydrocortisone sodium Succinate	10	10
Eudragit E 100	625	1250
Poly ethylene glycol 400	187.5	375
Isopropyl alcohol	6ml	6ml
Acetone	4ml	4ml

Table 2: COMPOSITION OF MUCOADHESIVE LAYER

Formulation code	M1 (mg)	M2 (mg)	M3 (mg)
Sodium alginate	300	_	_
Tamarind	_	200	_
Carbopol 940	_	_	80
HPMC	_	_	150
Glycerine	120	120	120
Distilled water	10ml	10ml	10ml

Table 3: COMPOSITION OF BUCCAL PATCHES

Formulation code	F1	F2	F3	F4	F5	F6
Drug matrix	D1	D2	D1	D2	D1	D2

formulation						
Mucoadhesive layer	**M1**	**M1**	**M2**	**M2**	**M3**	**M3**
Backing membrane	**EC**	**EC**	**EC**	**EC**	**EC**	**EC**

PHYSICO-CHEMICAL EVALUATION OF PATCHES

Weights:

Each patch was weighed individually on electronic balance and average weight of three patches was found.

Thickness:

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated.

Folding endurance of the patches:

Folding endurance of the patch was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on fivepatches.

Surface pH:

Buccal patches were left to swell for 2h o the surface of the agar plate, prepared by dissolving 2 %(w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then poured the solution into the petridish allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patches.

Drug content:

The patch allowed to dissolve 100ml isotonic phosphate buffer, pH 6.8. The amount of hydrocortisone sodium succinate in patch was measured spectrophotometrically at ƛmax of 249nm.

Swelling studies:

A drug loaded patch was weighed and kept in a 2% agar plate,after every 1 hour, the patch was removed and wiped with tissue paper and weighed upto 3 hrs. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

Tensile strength of the patches:

Tensile strength of the patch was determined with universal strength testing machine. The sensitivity of the machine is 1 gram. It consists of two load cell grips. The lower one is fixed and the upper one is movable. The test patch was fixed between the cell grips and the force was gradually till the film broke. The tensile of the patch was taken directly from the dial reading in kg[47, 48, 49].

In-vitro release studies of films by using dissolution apparatus:

The release study was carried out in a USP dissolution apparatus type VI .The dissolution medium was 500ml phosphate buffer pH 6.8 ,maintained at 37^0C and kept in a glass beaker fixed inside the USP dissolution flask.The patch was fixed to the central axis,which rotated at 50 rpm.Filtered samples 2ml were withdrawn at intervals of 30,60,90,120,180,240, and 300min.The concentration of drug released in the medium was assayed spectrophotometrically at 249 nm after suitable dilution with the dilution medium when necessary.

In-vitro buccal permeation study:

In vitro study of hydrocortisone sodium succinate permeation through goat buccal mucosa was performed using a modified glass diffusion cell.Goat buccal mucosa was obtained from a local slaughter house .Goat buccal mucosa mounted between the donor compartment and receptor compartment so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa;the donor compartment was filled with 15ml of phosphate buffer pH6.8.The donor compartment fixed such that it touches surface of receptor compartment(15ml capacity).The receptor compartment was

filled with phosphate buffer pH 7.4 and hydrodynamic in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. 2ml sample was withdrawn at specific time interval and analyzed for drug content at 249nm.The sample withdrawn was analyzed by UV spectrophotometer.

Ex-vivo mucoadhesion study:

Mucoadhesive strength of the patch was determined with universal strength testing machine. It consists of two load cell grips. The lower one is fixed and the upper one is movable. The test patch was fixed in the upper moved probe and the goat buccal mucosa was fixed in the lower cell which is moistened with the phosphate buffer pH6.8.The test patch was stucked to the lower side of the buccal mucosa. The mass required to detach the patches from the mucosal surface gave the measure of mucoadhesive strength[50, 51].

IN-VIVO COMPATABILITY STUDY :

Procedure for in-vivo compatibility study on human volunteers:

Informed conset was obtained from all human volunteers before conducting study. The study was conducted on 10 human volunteers. Volunters were given formulated hydrocortisone sodium succinate buccal patch and evaluate any discomfortable, heaviness or any irritations of the given patches.

Fig 6: Tensile strength tes using texture analyser

Fig 7: Invitro drug release in dissolution apparatus USPII

Fig 8: Mucoadhesion test using texture analyser

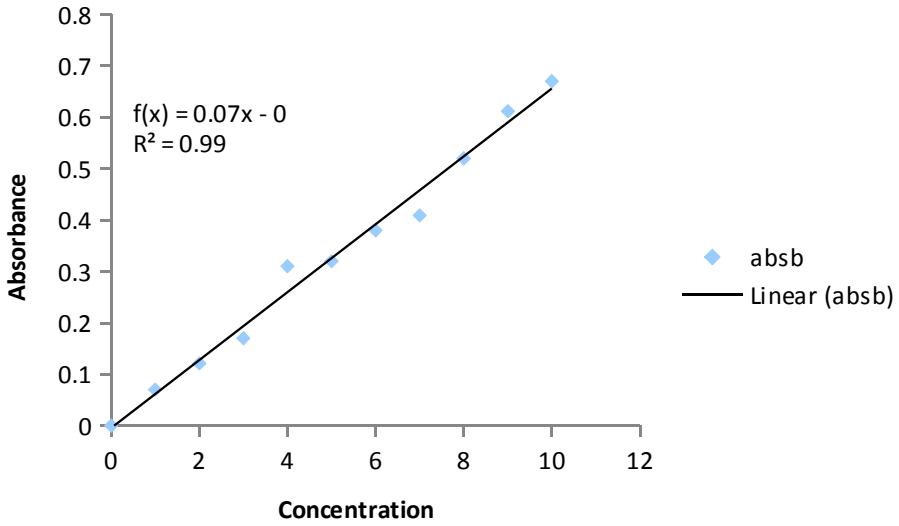
Fig 9: Ex-vivo permeation study

PREPARATION OF STANDARD CURVE OF HYDROCORTISONE SODIUM SUCCINATE.

Table 4: Absorbance values of Hydrocortisone sodium suucinate in phosphate buffer (pH 6.8)

Sl. no	Concentration (mcg/ml)	Absorbance
1	0	0
2	1	0.07
3	2	0.121
4	3	0.170
5	4	0.310
6	5	0.320
7	6	0.380
8	7	0.409
9	8	0.520
10	9	0.612
11	10	0.670

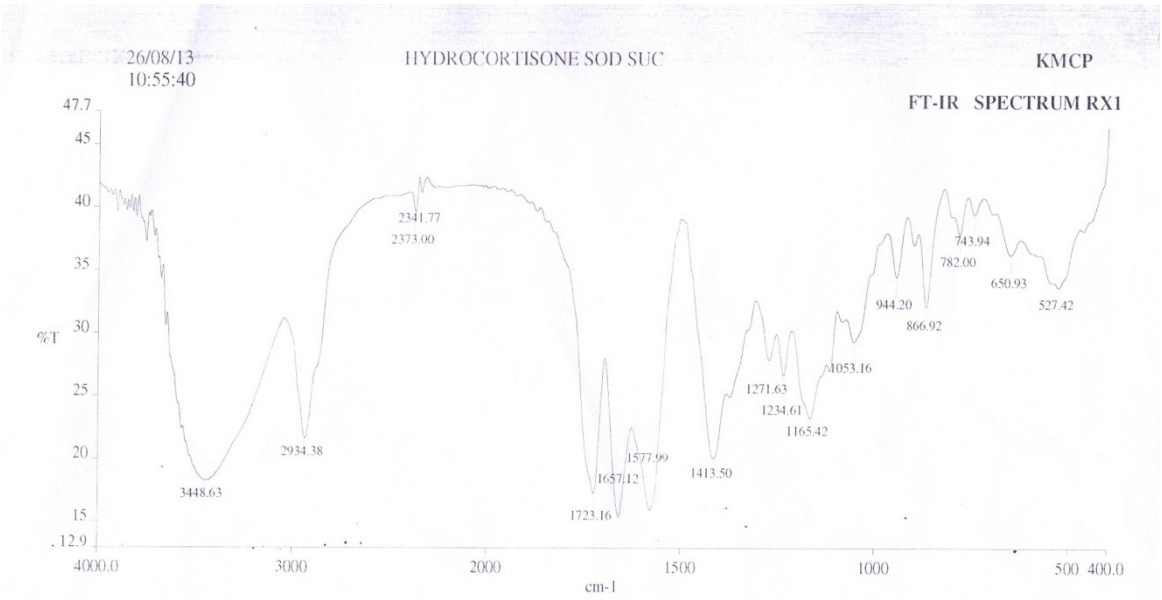
STANDARD GRAPH OF HYDROCORTISONE SODIUM SUCCINATE



Graph 1: Calibration curve of hydrocortisone sodium succinate

Drug- Excipient compatibility study

FT-IR Spectra for Hydrocortisone Sodium Succinate



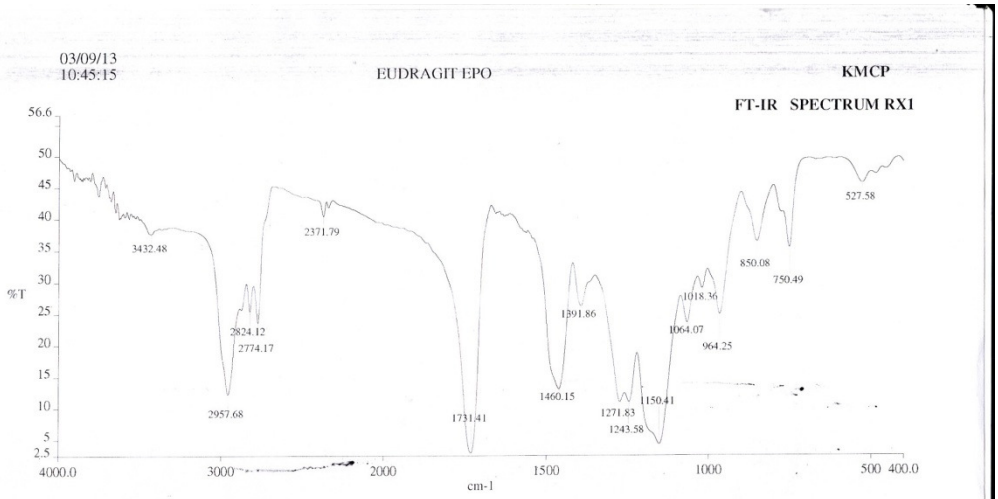
Spectrum Pathname: C:\PEL_DATA\SPECTRA\HYDROCORTISONE SODIUM SUCCINATE.002

HYDROCORTISONE SODIUM SUCCINATE.pk

HYDROCORTISONE SODIUM SUCCINATE.002 3601 4000.00 400.00 15.38 46.51 4.00 %T 4 1.00

REF 4000 41.89 2000 41.51 600
3906.12 39.62 3855.95 39.71 3823.19 39.61 3805.32 39.24 3753.96 37.24
3676.77 34.31 3651.80 30.58 3448.63 18.23 2934.38 21.63 2373.00 39.60
2341.77 41.14 1723.16 17.31 1657.12 15.38 1577.99 15.95 1413.50 20.07
1271.63 27.90 1234.61 26.67 1165.42 23.26 1053.16 29.33 944.20 34.49
866.92 32.13 782.00 37.86 743.94 39.45 650.93 36.24 527.42 33.67

FT-IR Spectra for Eudragit EPO



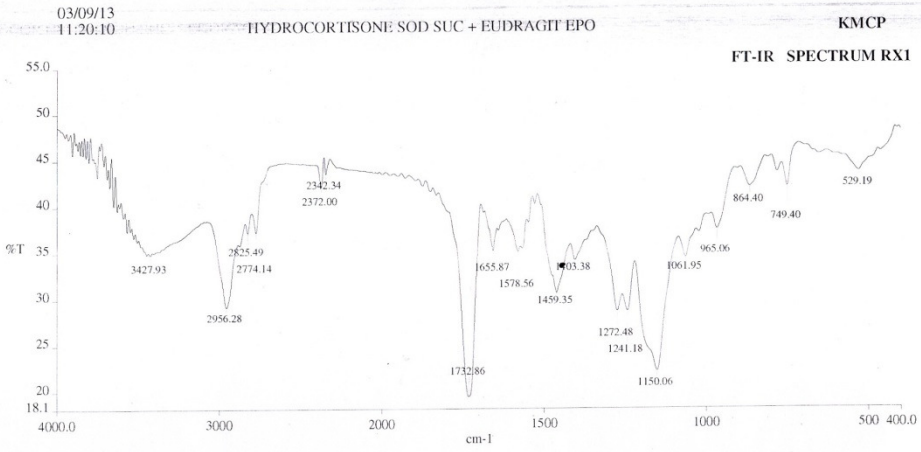
Spectrum Pathname: C:\PEL_DATA\SPECTRA\EUDRAGIT EPO.002

EUDRAGIT EPO.pk

EUDRAGIT EPO.002 3601 4000.00 400.00 2.93 49.72 4.00 %T 4 1.00

REF 4000 49.72 2000 39.17 600
3905.92 46.12 3855.57 46.11 3755.00 43.65 3679.95 42.88 3652.57 41.07
3629.90 40.01 3432.48 37.66 2957.68 12.26 2824.12 25.42 2774.17 23.63
2371.79 40.42 1731.41 2.93 1460.15 13.11 1391.86 26.21 1271.83 11.01
1243.58 11.03 1150.41 4.26 1064.07 23.59 1018.36 28.97 964.25 24.89
850.08 36.35 750.49 35.43 527.58 45.59

FT-IR Spectra for Hydrocortisone Sodium Succinate + Eudragit EPO



Spectrum Pathname: C:\PEL_DATA\SPECTRA\HYDROCORTISONE SOD SUC + EUDRAGIT EPO.002

HYDROCORTISONE SOD SUC + EUDRAGIT EPO.pk

HYDROCORTISONE SOD SUC + EUDRAGIT EPO.002 3601 4000.00 400.00 19.41 48.70 4.00 %T 4 1.00

REF 4000 48.70 2000 43.48 600
3906.56 45.59 3873.03 46.18 3856.62 45.64 3840.99 45.56 3823.72 45.33
3805.73 44.88 3754.27 43.23 3713.63 44.48 3693.57 43.10 3677.74 42.10
3654.45 40.11 3570.57 37.35 3427.93 34.85 2956.28 29.18 2825.49 37.18
2774.14 37.23 2372.00 42.05 2342.34 43.48 1732.86 19.41 1655.87 35.21
1578.56 35.10 1459.35 30.62 1403.38 34.17 1272.48 28.66 1241.18 28.68

PHYSICO-CHEMICAL EVALUATION OF PATCHES

Weight uniformity:

Weight uniformity for formulation D1 and D2 varied from 116 to 192mg and formulation F1 to F6 varied from 15.8 to 53mg. The patches were found to be weight uniform due to increasing the concentration of polymer.

Thickness:

As the total amount of polymer increases the thickness of the film were found to be increased. The thickness of the formulation D1 and D2 varied from 263 to 326µm and formulation F1 to F6 varied from 74 to 112µm, D2 having more thickness due to more concentration than D1.

Folding endurance

As the amount of plasticizer increases the folding endurance was found to be increases. All the patches exhibited folding endurance above 200 proving the flexible nature of patches due to the presence of the plasticizer.

Surface pH

The surface pH of the patches was between 5 to 5.5 which are due to the pH of the drug and polymer, hence no mucosal irritations was expected and ultimately achieves patient compliance.

Drug content

All the batches of the patches exhibit drug content within limit 86.28 to 91.06% which is within the desirable range due to the equal distribution of drug in the solution.

Swelling index.

Swelling of formulation was done on phosphate buffer pH 6.8 .In the formulation D1 and D2.

D2 having good swelling property than D1.In the mucoadhesive films, the swelling property more in carbapol and HPMC than others.

Table 5: Physicochemical evaluation of buccal patches

Formulation code	Weight uniformity(mg)	Thickness (µm)	Folding endurance	Surface pH	Content uniformity	Swelling index
D1	116 ±0.67	263±0.11	229±2	5.5±0.01	91.06±2.67	0.6257±0.2
D2	192±0.24	326±0.33	248±5	5.5±0.01	86.28±3	1.2793±0.14

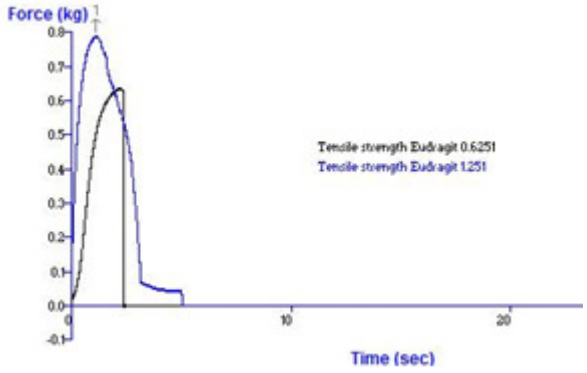
Table 6: Physicochemical evaluation of mucoadhesive films.

Formulation code	Weight uniformity(mg)	Thickness (µm)	Folding endurance	Swelling index
Sodium alginate	53±0.51	112±2	200±5	0.7623±0.13
Carbapol + HPMC	31.1±0.21	82±1	201±8	0.9718±0.21
Tamarind	15.8±0.011	74±1	219±3	0.5212±0.54

Table 7: Tensile strength

Formulation code	Extensibility (mm)	Tensile strength (N)

D1	**2.346**	**6.278**
D2	**1.234**	**7.747**



Graph 2: Tensile strength of D1 and D2.

IN-VITRO DRUG RELEASE

The results of drug release studies are presented in the table and the graphs

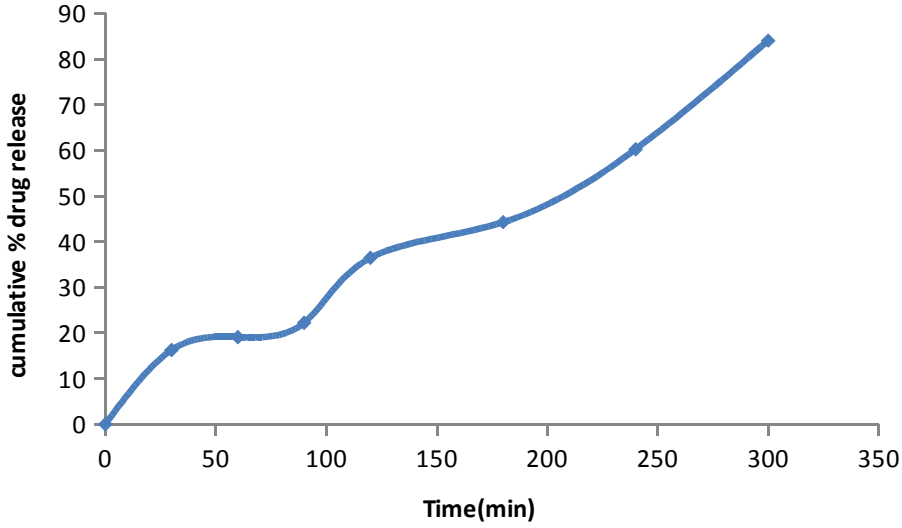
Hydrocortisone sodium succinate buccal patch were prepared with eudragit E100 polymer having different concentration. All the patches the drug released within 5hrs.

Here the drug release was carried out and concluded that the 0.625 gm of eudragit E 100 having 84% drug release within 5hrs than 74.36 % of the 1.25gm of eudragit E 100 polymer.

Table 8: In-vitro hydrocortisone sodium succinate release for batch D1

	Cumulative amount of drug release	**Cumulative% of drug**

Time (min)	(mg)	release
0	0	0
30	0.812	16.24
60	0.954	19.08
90	1.109	22.18
120	1.821	36.42
180	2.212	44.24
240	3.011	60.22
300	4.200	84

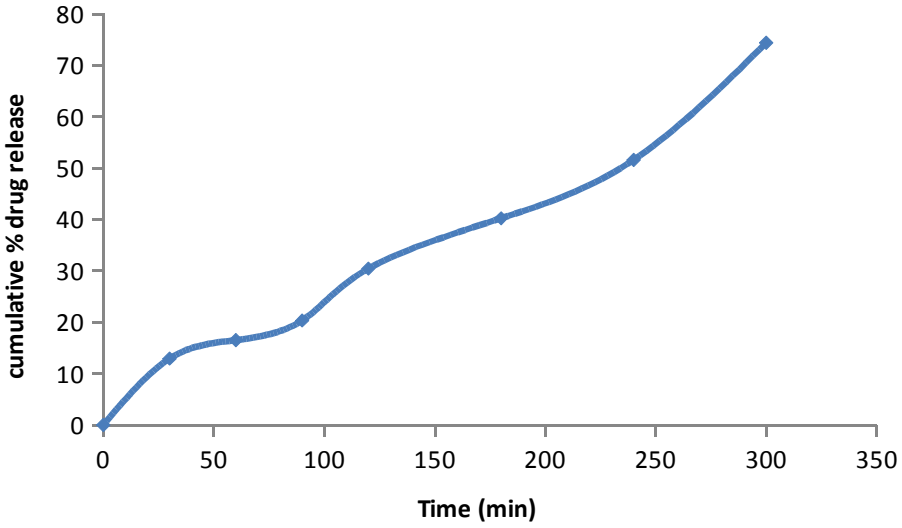


Graph 3: In-vitro drug release D1.

Table 9: In-vitro hydrocortisone sodium succinate release for batch D2

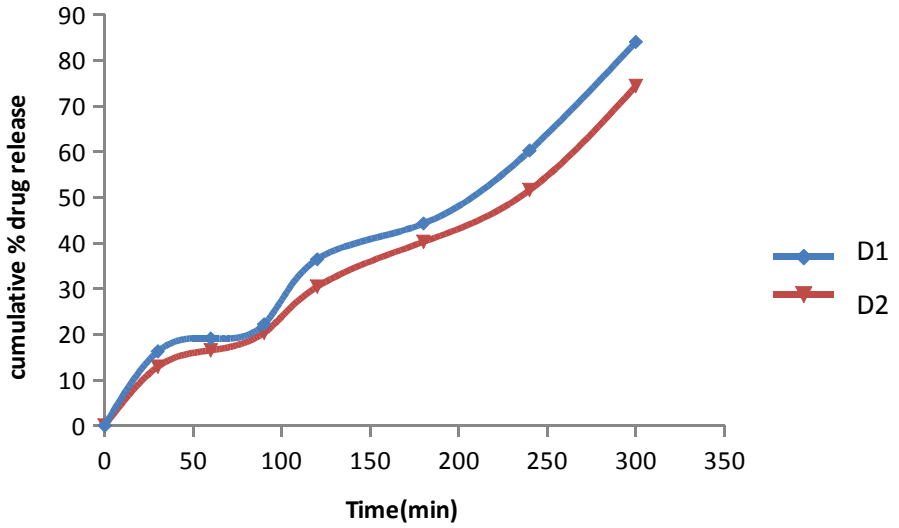
Time in minute	Amount of drug release (mg)	Cumulative % drug release
0	0	0
30	0.645	12.9
60	0.825	16.5

90	1.015	20.3
120	1.521	30.42
180	2.011	40.22
240	2.578	51.56
300	3.718	74.36



Graph 4: In-vitro drug release D2.

CUMULATIVE AMOUNT OF DRUG RELEASES FOR D1 AND D2



Graph 5: Correlation graph between D1 and D2

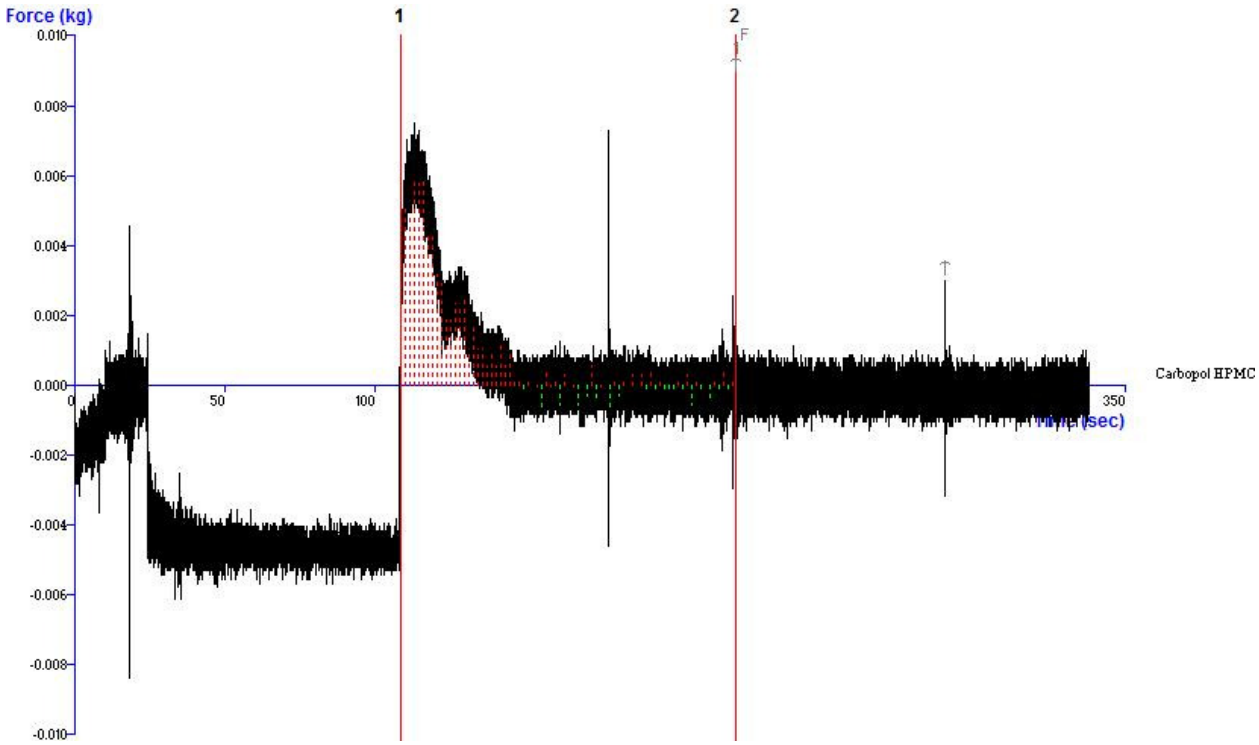
EVALUATION OF MUCOADHESION

CODE	Patch tested	ADHESIVE FORCE(N)	WORK OF ADHESION (N SEC)	DEBONDING DISTANCE (mm)
M3	Carbopol+HPMC	0.0873	0.98066	11.14
M1	Sodium alginate	0.016	0.0883	0.560
M2	Tamarind Gum	0.024	0.141	1.208

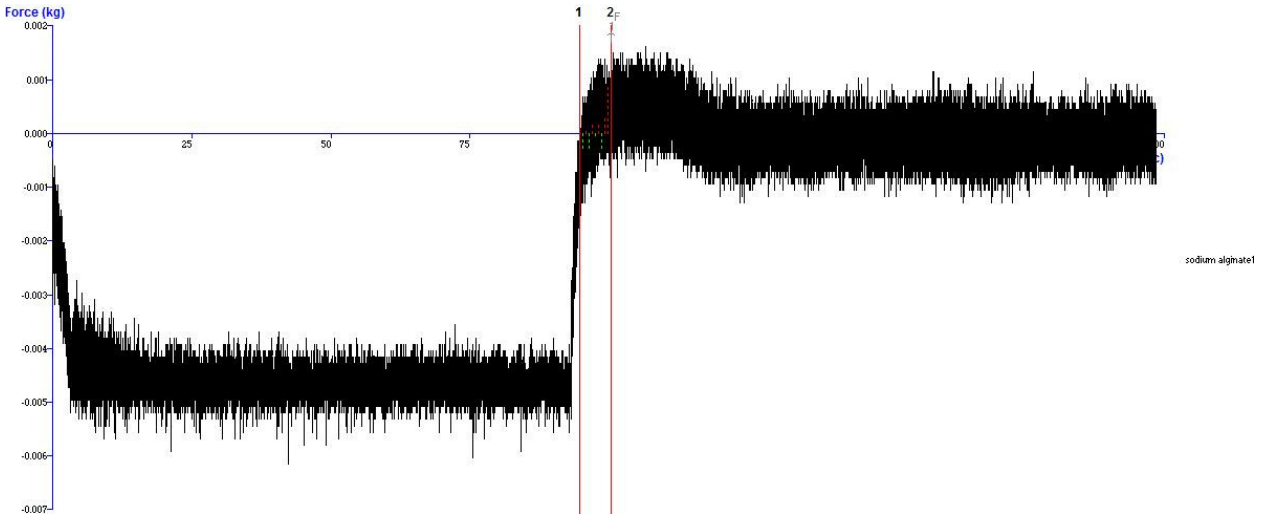
Table 10: Mucoadhesion was determined at 0.05N force and 90 sec contact time.

Patch tested	Applied force	Ahesive force (N)	Work of adhesion (N SEC)	Debonding Distances (mm)
Laminate	0.05	0.033	1.157	5.66
Laminate	0.1	0.039	1.177	6.004
Laminate	3.5	0.1667	1.883	4.072

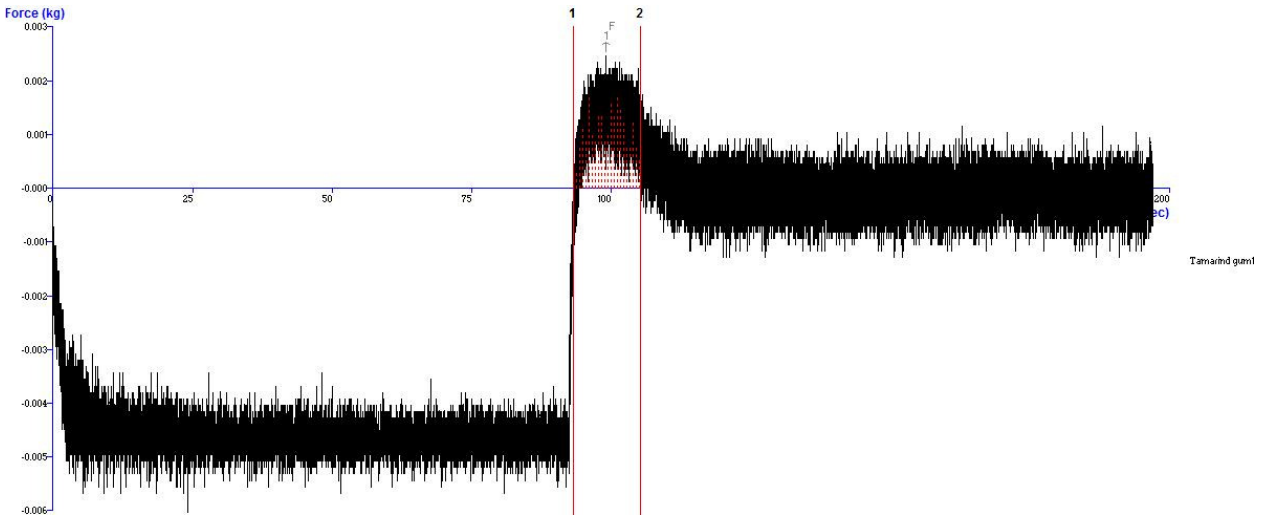
Table 11: Parameters of mucoadhesion testing with Texture analyser



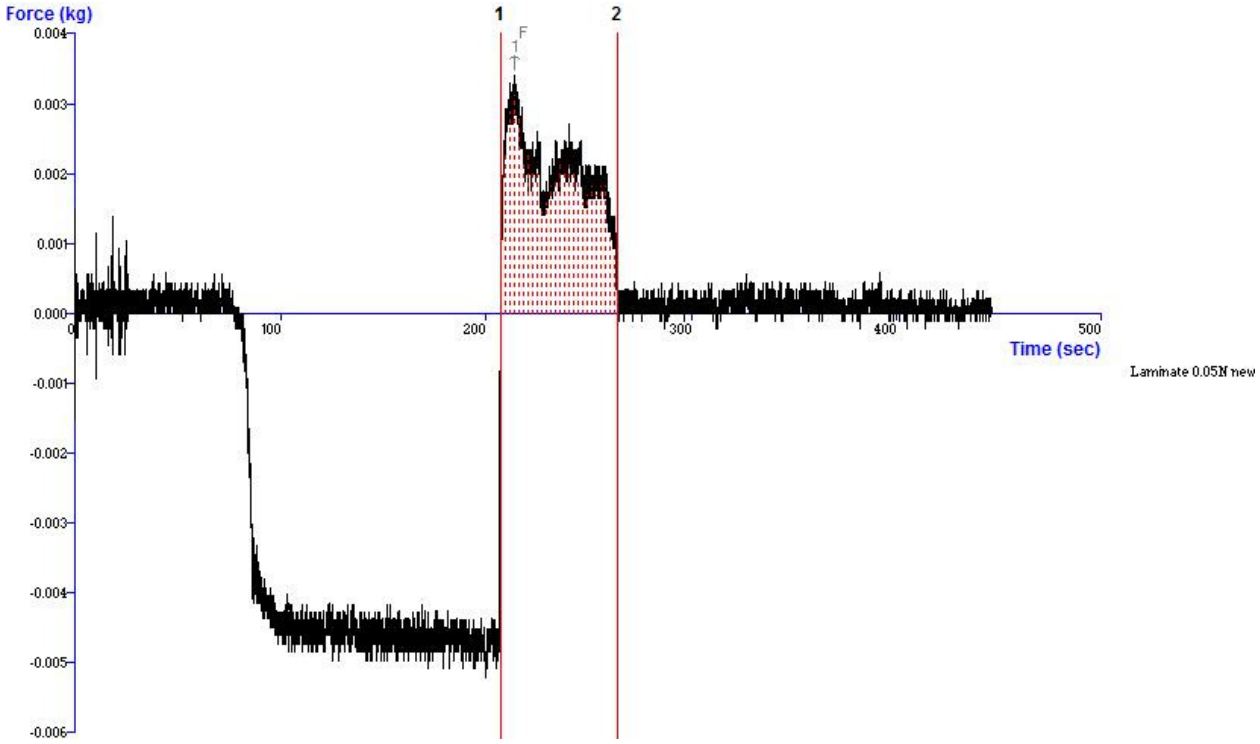
Graph 6: Graph of mucoadhesion of carbapol + HPMC



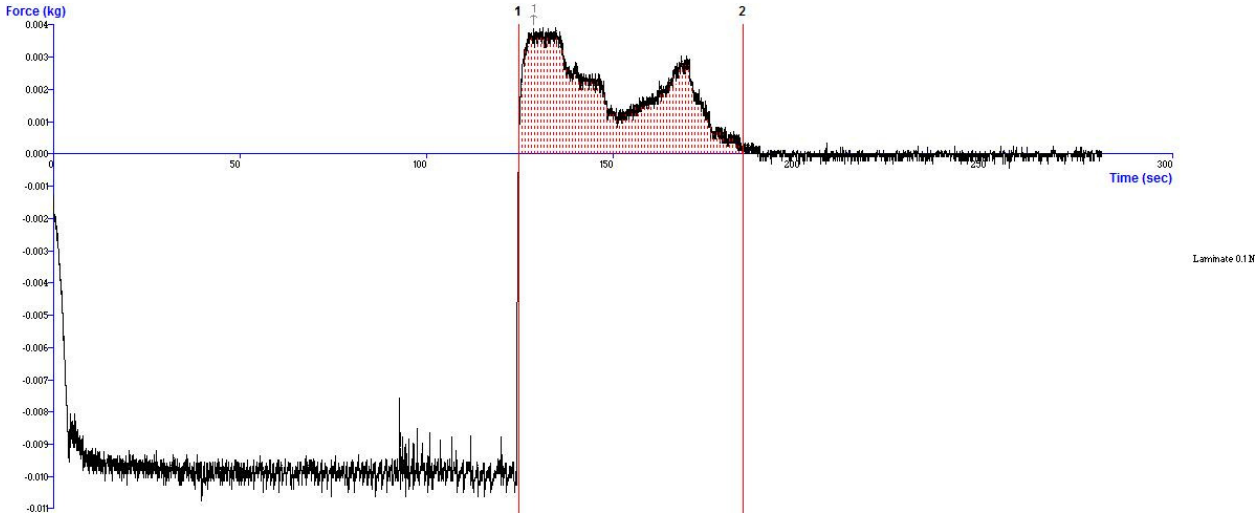
Graph 7: Graph of mucoadhesion of sodium alginate



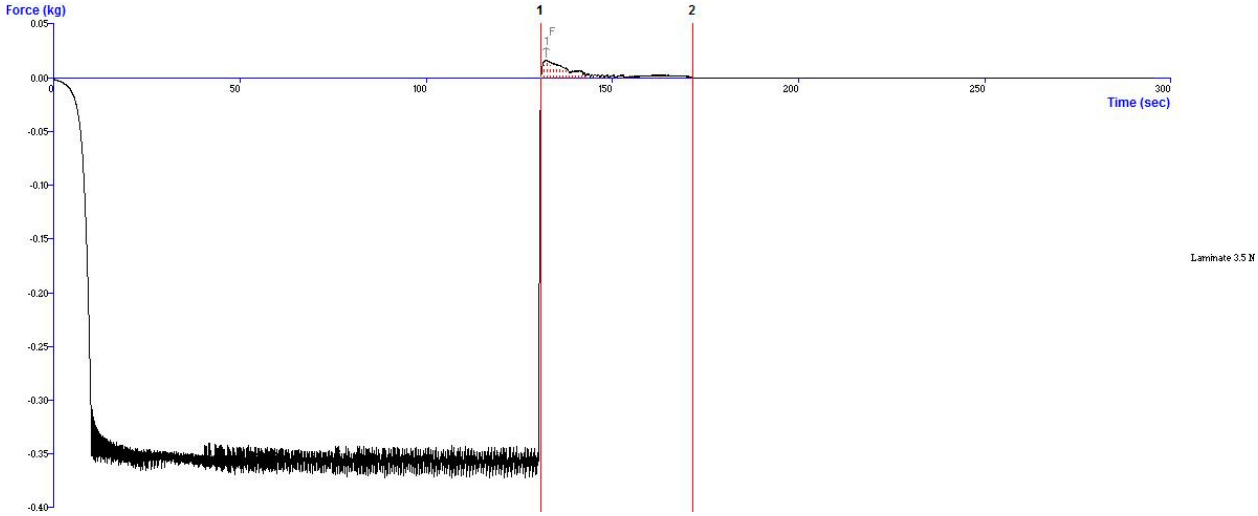
Graph 8: Graph of mucoadhesion of Tamarind.



Graph 9: Graph of mucoadhesion of laminte 0.05N.



Graph 10: Graph of mucoadhesion of laminate 0.1N



Graph 11: Graph of mucoadhesion of laminate 3.5N.

IN-VITRO BUCCAL PERMEATION STUDIES.

In-vitro buccal permeation study was carried out , the permeation study was carried out by using freshly excised goat buccal mucous membrane. The in-vitro drug permeation was 76% for 4hrs in F5 formulation.

Table 12: Invitro hydrocortisone sodium succinate permeation for batch F1.

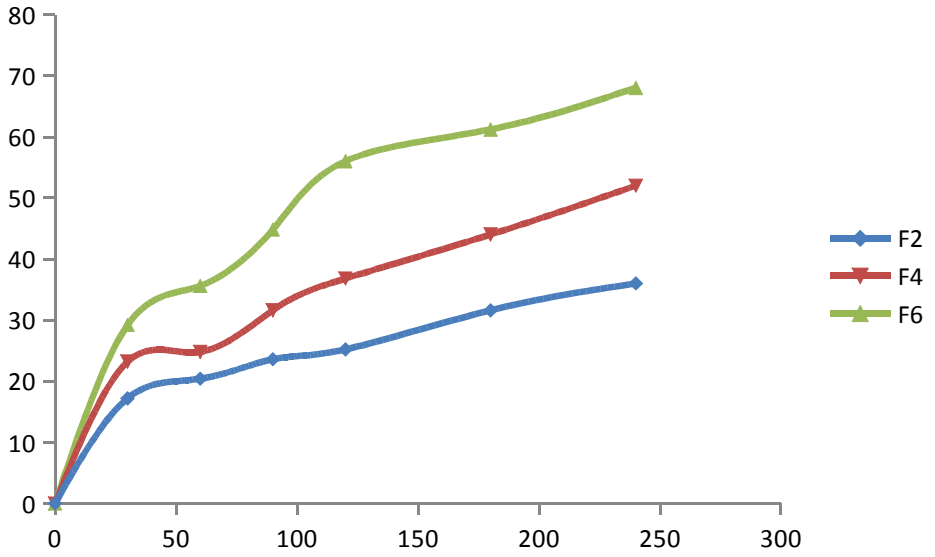
Time in minute	Amount of drug release (mg)	Cumulative % drug release
0	0	0
30	0.54	21.6
60	0.65	26
90	0.71	28.4
120	0.83	33.2
180	0.92	36.8
240	1.2	48

Table 13: Invitro drug permeation for batch F3

Time in minute	Amount of drug release (mg)	Cumulative % drug Release
0	0	0
30	0.59	23.6
60	0.71	28.4
90	0.88	35.2
120	0.97	38.8
180	1.23	49.2
240	1.30	52

Table 14: Invitro drug permeation of drug for batch F5

Time in minute	Amount of drug release (mg)	Cumulative % drug Release
0	0	0
30	0.83	33.2
60	1.03	41.2
90	1.27	50.8
120	1.58	63.2
180	1.79	71.6
240	1.90	76



Graph 12: Correlation of the invitro permeation for F1, F3 AND F5.

Table 15: Invitro drug permeation for batch F2.

Time in minute	Amount of drug release (mg)	Cumulative % drug Release
0	0	0
30	0.43	17.2
60	0.51	20.4
90	0.59	23.6
120	0.63	25.2
180	0.79	31.6
240	0.90	36

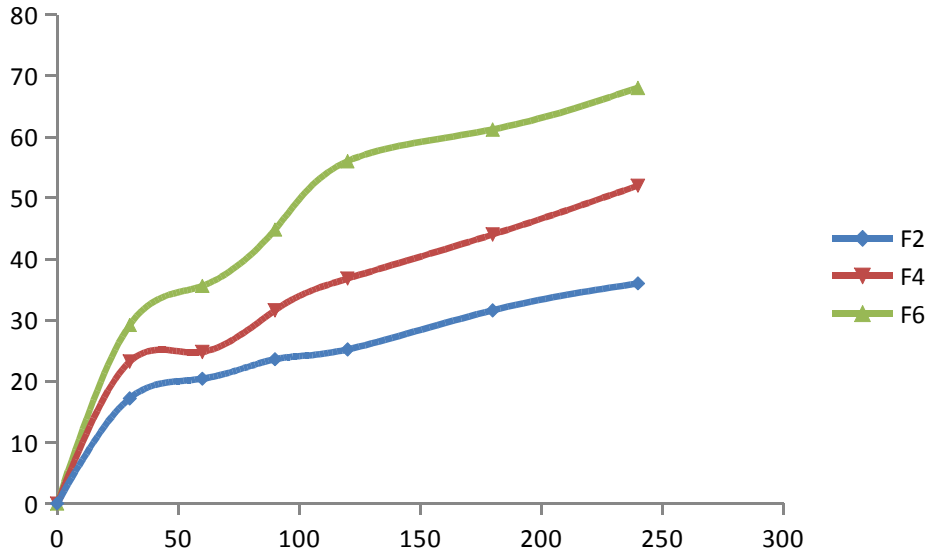
Table 16: Invitro drug permeation for batch F4

Time in minute	Amount of drug release	Cumulative % drug

	(mg)	Release
0	0	0
30	0.58	23.2
60	0.62	24.8
90	0.79	31.6
120	0.92	36.8
180	1.10	44
240	1.30	52

Table 17: Invitro drug permeation for batch F6

Time in minute	Amount of drug release (mg)	Cumulative % drug Release
0	0	0
30	0.73	29.2
60	0.89	35.6
90	1.12	44.8
120	1.40	56
180	1.53	61.2
240	1.70	68



Graph 13: Correlation of the invitro permeation study for the batch F2, F4 and F6.

INVIVO COMPATABILITY STUDIES.

Invivo evaluation of the buccal patches in human healthy volunteers revealed that no irritations, no heaviness and good mouth feel was observed. This further confirms successful formulation of hydrocortisone sodium succinate in the form of buccal patch. None of the formulations were detached from the oral mucosa over the study period, which indicated that the bioadhesion values of the formulations were satisfactory to retain the film on the buccal mucosa.

SUMMARY AND CONCLUSIONS

Buccal tablets , lozenges and pastes are used in relieving pain, inflammation associated with oral mucosal diseases like inflammations, oral submucous fibrosis, ulcer, and other lesions. Hydrocortisone sodium succinate is used as an anti inflammatory agent.

The most important advantage of the mucoadhesive buccal films is that it contains a lower drug dose, adequate for therapeutic effect as it is placed directly on the site of the inflammation, when compared to conventional administration. Moreover, mucoadhesive buccal patches are convenient and comfortable to use as they are non-irritant and self administration is possible.

In the present work successful attempt was made to formulate buccal strips using 10 mg drug loaded in eudragit E100 polymer and PEG 400 is used as a plasticizer. The formulations are D1 and D2, D1 was to releases 84 % of drug within 5hrs.In the formulations D1 and D2 carried all the physicochemical evaluations and it was found to be within the limits.

In the formulations F1, F2, F3, ,F5 and F6 the in-vitro diffusion study was carried out, the F5 showed maximum drug permeation through the buccal mucosa of the goat. All the physico chemical parameters done in this formulations and it was found to be within the limits.

The optimized formula F5 was carried out the in-vivo compatibility study it was not found that to produce irritation, discomfort able or heaviness. This F5 was detached from the oral mucosa over the study period

The FTIR characterization of hydrocortisone sodium succinate with Eudragit E 100 blend indicates no interaction between them.

Thus present attempt of developing hydrocortisone sodium succinate buccal patch laminate has been ac.omplished with satisfactory results.

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